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WASP VENOM ALLERGY AND IMMUNITY

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THE dual purpose of this three-year study was to develop a safe and effective immunization procedure for individuals with a history of severe reaction to wasp sting, and to evaluate diagnostic tests of the skin and conjunctiva by means of controlled studies in normal individuals. It was also possible in a limited way to observe the acute manifestations of venom allergy, and to examine the antigenic relationships among several varieties of wasp.

According to two reviews,[1,2] clinical immunity against hymenoptera (wasps, bees, ants et cetera) has been achieved in a limited number of individuals by the injection of graduated amounts of whole body extract as well as by the accidental or planned intermittent stings of live insects. In order to limit the number of components in the immunizing material while at the same time controlling the volume administered, we have introduced the use of wasp venom (free of other body constituents and of adhering contaminants, such as pollen), the unit of antigen being temporarily the surgically removed venom sac. Our earlier experience with whole body extract will also be briefly presented.

MATERIAL AND METHODS

Each autumn live wasps are procured either individually in the field with butterfly nets or, preferably, in intact hives so that uniformity of species is assured. Individual insects are anesthetized lightly with ether in the laboratory so that venom sacs can be aseptically removed by surgical dissection. After the sacs have been placed in small sterile tubes, sufficient

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autoclaved glycerin is added to barely cover them, the volume being recorded. Groups of one to twenty sacs are stored at 4° C until the following spring when they are used for tests and immunization. That this type of handling maintains the original activity for one year (but apparently not for two years) has been established by ancillary studies in the skin and eye which compared the activity of stored sacs with that of freshly removed venom. Since, however, diluted material showed a definite reduction in potency within two days, stored sacs were crushed only an hour or two before use. At this time, the released venom was diluted in isotonic saline solution so as to provide strengths ranging from .001 to 15 sacs per one-tenth ml.

Standardizing the antigen in this manner rested on the presently necessary assumption that each venom sac contains a uniform amount of activity. The risk of variation among individual sacs was minimized by utilizing from 10 to 100 sacs as the starting material for a given series of dilutions. A rough idea of the relationship in potency between our testing materials and the natural sting of the insect was obtained by conducting concurrent intracutaneous and deliberate sting tests in normal individuals.

Intracutaneous Tests utilized .01 ml of venom in a series of strengths which elicited responses ranging from negative to strong positive. A wheal of 1 cm diameter surrounded by an erythematous flare 3 cm wide was recorded as +++, while reactions of smaller size were termed ++ and +, all readings being made at twenty minutes. The minimal, or threshold, response was used as the basis of all comparisons. Tests were repeated during and after the termination of the course.

Conjunctival Tests employed .02 ml of antigen and commenced with a strength of 0.1 sac/.1 ml (actual dose, 0.02 sac). At five minute intervals doubling concentrations were instilled until minimal reddening of the caruncle developed, representing the threshold response. One additional tube of antigen was then tested so as to confirm this delicate endpoint by evoking mild erythema of the bulbar conjunctiva and pruritus. The conjunctival sac was then irrigated with isotonic saline solution, a few drops of 1:1000 epinephrine finally being introduced to negate the reaction.

Serological Tests.—Passive transference studies were carried out with sera of most of the patients to demonstrate sensitizing antibodies for bee and wasp venom in the skin of normal subjects. Cross-tests between various venoms were done by preparing replicate areas of normal skin with mixtures of sensitizing serum and an excess of one or another venom. In twenty-four hours, successive sites were challenged with each of the venoms. Whereas the homologous venom proved to be inactive, certain others lit up the site, indicating their possession of different specificity.

Deliberate Sting Tests.—In a number of instances patients consented to be stung, on the volar surface of the forearm, with the type of insect

which had caused their severe reactions, and sometimes with others as well. As during therapeutic courses, continuous observations were made throughout such experiments of the blood pressure, pulse, and local as well as any systemic manifestations. To date, such tests have been attempted only after a course of immunization because of the risk of anaphylaxis in the untreated subject.

Wasp-Allergic Subjects.—Of the ten patients treated for one or more years with venom, seven gave a history of developing unconsciousness within one to fifty minutes (usually fifteen minutes) after the sting of a yellow jacket *(vespula maculifrons)*. This had been preceded by generalized urticaria and/or pruritus and was often associated with such conditions as tachycardia, palpitation, bradycardia, dyspnea, cyanosis, fever, great apprehension, violent headache, and acute gastrointestinal disturbances. The three remaining subjects had experienced marked localized and generalized urticaria with prolonged malaise after being stung by *vespula maculifrons* in two cases and polistes in the other. One wasp-allergic subject, HOU, had also collapsed after a honeybee sting. Brief reference will be made to three additional subjects with histories of collapse after yellow jacket stings who were treated prior to 1953 when immunization was carried out with whole body extract.

Immunization Procedure.—The sequence of venom dosage depended on the localized and systemic responses to individual injections. The total amounts of venom given were empirical, ranging from sixteen to twenty-seven venom sacs per patient in 1953 and 1954, whereas by 1955 courses were generally restricted to six sacs. The schedule of dosage had by this time also become more or less standardized for the small group. Courses which were initially planned for two or three annual visits were restricted to one by 1955. The intracutaneous route was uniformly employed for all injections.

Immunity was judged by intracutaneous, conjunctival and sting tests as well as by the limits of tolerance for injected antigen.

Overdose Reactions to therapeutic injections in three instances reproduced the patient's clinical syndrome. These will be described in detail below.

RESULTS

Tests on Control Subjects.—A group of thirty-four young adults, who had never experienced a wasp sting or had exhibited only the transitory localized pain and inflammatory response which are characteristic of unsensitized individuals, were tested by the routine intracutaneous and conjunctival procedures. Of this group, twenty-one were examined concurrently with a uniform batch of yellow-jacket venom obtained from *vespula maculifrons* workers. On the same day, each was subjected to the sting of a live yellow jacket worker. This enabled us to estimate the amount of venom injected by the insect during the three minute stinging

TABLE I. REACTIVITY OF 21 NORMAL SUBJECTS TO VENOM OF YELLOW-JACKET WORKER WASP

As Judged by Concurrent Intracutaneous, Conjunctival and Three-Minute Sting Tests

Subject	Conjunctival Test* with .02 ml Threshold Dose (sac/.1 ml)	Intracutaneous Test* with .01 ml Threshold Dose (sac/.1 ml)	Insect-Sting Estimated Amount Injected** (sacs)
1. DAV	0.5	0.003	0.1
2. RYA	1.0	0.025	0.05
3. BER	2.5	0.1	0.1
4. DIE	2.5	0.25	0.1
5. DON	2.5	0.25	0.2
6. VAN	2.5	0.25	0.25
7. QUE	2.5	0.5	0.1
8. LAN	3.8	0.006	0.25
9. KRI	3.8	0.5	0.1
10. ZIC	3.8	0.006	0.03
11. FAC	5.0	0.25	0.1
12. DUE	5.0	0.006	0.05
13. COA	5.0	0.25	.25
14. McC	10.0	2.5	0.5
15. CAR	10.0	0.25	0.5
16. CHA	10.0	0.01	0.1
17. FRA	10.0	0.006	0.2
18. STA	10.0	0.25	1.0
19. EVA	15.0	0.5	0.2
20. BIL	15.0	1.0	0.25
21. KON	15.0	0.01	0.01
Range	0.5 to 15	.003 to 2.5	.01 to 1.0
Median	5	.25	0.1

*To determine minimal reactive strength.
**Wheal and flare which followed stinging was compared with those evoked by intracutaneous tests with known amounts of venom.

period, the resulting wheal-and-flare reaction being compared with those evoked by the testing solutions. The estimates presented in the fourth column of Table I were made as follows:

The reaction provoked by the insect was matched with one produced by our intracutaneous tests. The strength of venom associated with the latter was then multiplied by the volume used (0.01 ml) to give an absolute figure for the amount of venom involved. Patient DAV, for example, developed within twenty minutes after being stung on his forearm, a wheal-and-flare reaction which duplicated that elicited by the intracutaneous injection of .01 ml of solution containing 1 sac/.1 ml. Since the venom involved in the latter test amounts to about one-tenth of the contents of the original venom sac, one can estimate that the insect also injected about one-tenth of its sacful of material, assuming the sacs to be roughly uniform.

It will be noted that the amount of venom required for the threshold responses by the intracutaneous route was decidedly less than the amounts estimated to have been injected by the insect. Subject DAV, for example, required only .01 ml of .003 sac/.1 ml for his minimal response, the absolute amount being .0003 sac. The insect, however, appeared to inject about 300 times this requirement. The estimated proportion of the total sac contents which was injected into the various normal subjects by successive wasps varied from 1/100th of the sac to the entire contents, the median value being .1 sac as shown at the bottom of Table I. Cor-

TABLE II. REACTIVITY OF WASP-ALLERGIC SUBJECTS TO TESTS AND TO INSECT STINGS

Patient	Year	Venom Required for Threshold Response					Insect Stings after Course		
		Before Immunization		After Immunization					
		Eye Test (sac/.1 ml)	Endermal Test (sac/.1 ml)	Days	Eye Test (sac/.1ml)	Endermal Test (sac/.1ml)	Laboratory	Field	Systemic Reaction
WIL	1955	0.25	.05	84	1.0	.125	1 frons W.*		none
NEL	1955	0.25	.006	120	5.0	.05	2 frons W.*		none
SAU	1953	0.57Q†	.001Q	90	5.0Q	.01Q		1 frons W.	none
	1954	0.5	.006					1 bumblebee	none
								1 frons W.	none
								1 unident.	none
	1955	0.5	.006						
PER	1954	1.0	.025	19	4.0	.25			
	1955	1.5	.05						
HOU	1953	0.67Q	.003Q	80	1.0Q	.25Q	1 frons W.		none
	1954	1.0	.003	120	2.0	.025	1 honeybee		none
				127			1 bumblebee		none
							1 honeybee		none
	1955	1.0	.006	110	2.0	.05	1 frons W.		none
FIE	1954	1.0	.01	8	2.5	.1			
ARV	1953	1.00Q	.001Q	135	7.5Q	.05Q			
	1954	1.0	.01	6	5.0	.05		1 honeybee	none
	1955	1.5	.006	120	5.0	.012		1 bumblebee	none
BAK	1954	2.5	.009	8	15.0	.1	1 honeybee		none
	1955	2.5	.013	118	3.8	.025			
KRO	1954	1.0	.05	30	2.0	.25			
Range		.25 to 2.5	.003 to 0.1		1.0 to 15.0	.003 to .3			
Median		1.0	.01		3.8	.06			
GUTH**	1955	1.5	.1	15	2.5	.1	2 polistes		none

*Vespula maculifrons worker.
**Polistes-allergic and polistes tested. (Vespula maculifrons was the allergen for all other patients.)
Q† =queen insect.

responding values for the threshold intracutaneous tests ranged from .003 to 2.5 sacs/.1 ml with a median figure of .25 sacs/.1 ml.

Much higher concentrations of the standard testing solutions were required to elicit minimal reactions in the conjunctivae of these normal subjects, a strength of from .5 to 15 sacs/.1 ml being required with a median value of 5 sacs/.1 ml. Making allowance for volume, this means that the median subject required the contents of one full venom sac for his minimal conjunctival response. This is forty times more than the amount needed by the median subject for a threshold response to intracutaneous test.

The thirteen other nonallergic members of the control group were tested as above, with the exception that conjunctival tests were omitted in eight and stinging by wasps was not included. Results were comparable with those listed on Table I.

Tests on Wasp-Allergic Subjects.—Table II presents data analagous to those of Table I, the thresholds of reactivity being determined by conjunctival and endermal tests before and again after courses of immunization with wasp venom completed during 1953, 1954, and 1955. It will be noted that the median requirement for individuals allergic to yellow jacket was 1 sac/.1 ml in the conjunctival test—one-fifth that of the control group. Similarly the endermal test provided minimal whealing in the median patient when a strength of .01 sac/.1 ml was employed. This

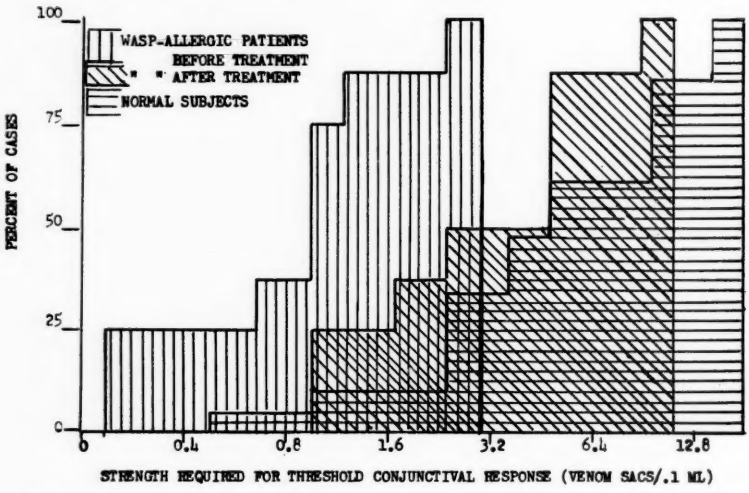

Fig. 1. Susceptibility of conjunctiva to yellow jacket venom. (Allergic patients before and after immunization, compared with normal subjects.)

was about 1/25 that associated with the test in the corresponding control subject. As the histogram shows in Figure 1, the threshold values for the conjunctival test of the patient following therapy shifted toward and into the zone occupied by the control data.

That conjunctival immunity was associated with clinical immunity was revealed by the negative systemic response of seven of these patients who were stung accidentally or deliberately by one or more hymenoptera (see Table II). Patient HOU, for example, not only submitted to stings with a vespid in 1953 and 1955, but with a honeybee in 1954. Seven days later she permitted us to apply a bumblebee and also a honeybee. Two other patients were stung with *vespula maculifrons* workers against the venom of which they had been immunized three or four months earlier. Patient GUTH who had received polistes antigen submitted to stings with two polistes within an hour's time two weeks following his course with venom sacs removed from paper wasps. BAK tolerated well the sting of a honeybee eight days after his therapy with yellow jacket venom. All these patients developed wheal-and-flare reactions comparable to those exhibited by our normal subjects under a similar situation and showed no significant change in blood pressure or pulse rate throughout the experiment. Two patients were accidentally stung on several occasions by bees and wasps without untoward effect.

IMMUNIZATION SCHEDULES

Venom. Table III presents for nine patients the successive doses involved in single visit courses prescribed in 1955. The first two or three

TABLE III. SINGLE-VISIT IMMUNIZATION COURSE USED FOR NINE WASP-ALLERGIC SUBJECTS IN 1955
(Dose expressed in Venom Sacs)

Time (min.)	WIL	WAL	NEL	BAK	PER	ARV	HOU	SAU	GUTH†
0-15	0.42	0.34	0.12	0.02	0.17	0.17	0.07	0.43	(0.17)
30	0.04	(0.32)*		0.05	(0.17)	(0.22)	(0.01)	(0.17)	0.17
45					0.11		0.1	(0.37)	
60			0.28	0.1	0.36	0.25		(0.18)	(0.42)
75		0.75		(0.07)	0.57				
90				0.25	0.5		(0.23)		0.25
105		0.6			1.36	0.5	0.25	0.75	
120	lunch			0.5				1.38	0.46
135		1.05	0.75	0.75	1.59	0.75	0.5	1.5	0.82
150	0.02	(0.44)			1.63	1.5			
165	(0.4)	1.47		1.5		(0.67)	0.75	1.5	
180			0.85	lunch	left	1.5	lunch	lunch	1.4
195	(0.92)	1.74		1.5		2.24			
210		left	1.0	1.5			1.5	2.0	1.46
225	0.5		lunch			left		2.0	1.55
240	0.75			left			1.5		left
265	1.5						1.38	left	
270			1.53				(0.41)		
285	1.5								
300	1.2		1.5				left		
Total tests	5.93 (1.32)*	5.95 (0.76)	6.03	6.17 (0.07)	6.29 (0.17)	6.31 (0.89)	6.05 (0.65)	9.56 (0.72)	6.11 (0.59)

†Polistes-allergic and polistes-immunized. All others clinically reactive and treated with yellow jacket (vespula maculifrons worker insects).
*Intracutaneous tests done with other hymenoptera venoms (polistes, honeybee, bumblebee, bald-faced hornet workers).

figures apply to intracutaneous tests, those carried out with *hymenoptera* other than the one selected for therapy being bracketed. GUTH was the only subject treated with paper wasp (polistes) venom, the rest receiving yellow jacket *(vespula maculifrons)* worker's venom. The courses were comprised of the contents of from 6 to 9.6 sacs, and were completed within five hours or less, usually including a half hour for lunch. There were no untoward reactions.

Sacs removed from live yellow jackets had also been the source of therapeutic venom in the two preceding years. Since this form of antigen had never been used before and its protective qualities as well as the potency of this unit of dosage had not been established, individuals to receive it in 1953 were asked to come on two or three occasions for divided doses, one to seven days apart. During their initial visits, ARV, SAU and HOU received a series of small injections during several hours which brought the total doses to 1, 2.25 and 7.75 sacs of venom, respectively. Only queen insects were available for the purpose. During a long second visit, they received four, six, and twelve sacs, respectively. In a third session 11.6 sacs were given ARV, while SAU took eight sacs. Thus the totals for the year come to 16.6, 16.25 and 19.75.

By 1954 the group had acquired seven members, three of whom completed a course of fifteen to twenty sacs of yellow jacket venom in two visits one or two weeks apart, while the remaining four received between 6.3 and 21 sacs during a single, prolonged visit.

Whole Body Extracts.—Although this report deals primarily with venom as the immunizing medium, our earlier experience with whole body extracts of *v. maculifrons* will be presented briefly at this point. Thirteen courses were given to six individuals, all of whom had experienced collapse after yellow jacket stings and three of whom were later given courses of extirpated venom. Between the years of 1948 and 1952 these patients received total amounts of body extract ranging from 12,500 to 32,500 protein N units (.125 to .325 mg phosphotungstic-acid-precipitable N) annually in one or two long visits. Such therapy increased their conjunctival tolerance by as much as tenfold and raised the intracutaneous threshold requirements by twofold.

The first attempts to evaluate immunity by means of yellow jacket stings with live insects were made in 1950 in patients HOU and SAU two months after their completion of a course of 15,000 protein N units of whole body extract. Both stated that they experienced transitory, mild prodromata such as had preceded their original, anaphylactic reactions, SAU developing flushing, tachycardia, nasal obstruction and headache while HOU noted tingling of the palms and soles. There was an associated acute reduction in diastolic pressure in SAU to 38, and a ten point reduction in systolic pressure. HOU, on the other hand, showed a ten point rise in systolic pressure for a few minutes. The recovery to normal was spontaneous and rapid. The insects were large, live queens, held in the stinging position for sixty seconds in the case of SAU and for fifteen minutes in the other patient.

SAU received an accidental sting with a polistes wasp nine months after his 10,000 unit course of body extract in 1951 and suffered only mild, localized discomfort. None of the other five patients was stung during these early years on whole body extract therapy, with the exception of HOU whose initial course was given with commercial, lyophilized beesting. After reaching a cumulative total dose of twenty-three stingers during a five-and-one-half-month period, she showed a seventy-fold heightening of cutaneous resistance to this antigen and tolerated, with only slight tingling of the fingers and a fifteen point drop in blood pressure readings, the deliberate stings of two honeybees. Prior to this course, HOU had collapsed after being stung by a honeybee on one occasion and by a yellow jacket wasp on another.

In an attempt to relate these data with whole body extract to the corresponding ones for venom, eighty sacs of yellow jacket venom were subjected to chemical assay. After their extirpation from live workers, the sacs were crushed and clarified by centrifugation, two washings of the sediment being added to the supernate. The average sac was found to contain 0.0036 mg phosphotungstic-acid-precipitable N and 0.0027 mg nonprecipitable N in its venom. By comparing the threshold requirements of a given patient with the two types of antigen (in different years, prior to therapy), it was possible to estimate the relative activities of the

body and the venom sac antigens. On a precipitable N basis, venom appeared to be from three and one-half to five times more active. This was no doubt due to the inclusion of other than allergenic protein in the whole body extract.

IMMUNITY AS JUDGED BY TOLERANCE OF ALLERGIC SUBJECTS FOR INJECTED ANTIGEN

In order to elaborate a safe, short and effective procedure for immunization, it was of value to learn the limits of tolerance of each patient for injected venom. In most instances, this was accomplished with only slight systemic reactions. In three patients, however, the manifestations approximated (briefly) those described by the subject for his accidental stinging episode. Since little is known of this anaphylactic-like syndrome in man, details will be presented.

In 1953 SAU developed a sense of lightheadedness, headache and flushing ten minutes after he had completed his day's course of 2.25 sacs of yellow jacket queen venom. He shortly complained of tachycardia, pounding in his head and chest, and generalized heat and throbbing in his skin. His nasal passages became congested, he became apprehensive and felt cold in a warm room. His pulse rate rose to 160 and for a moment his diastolic blood pressure could not be obtained. There appeared to be mild cyanosis of the face. An intramuscular injection of 0.25 ml of 1:1000 epinephrine, our standard dose for systemic reactions, brought prompt relief of all symptoms except an intense headache, which yielded gradually to acetylsalicylic acid. During two mild reactions of this type following injections on the next two days, the pulse rate was observed to rise while both the systolic and diastolic readings fell moderately for a few minutes. An electrocardiograph recording showed no abnormality except tachycardia during the more decided of these reactions which was associated with a wide pulse pressure (diastolic pressure being reduced to 40 while the systolic pressure dropped fifteen points.) On this occasion, SAU had received a total of 6.5 venom sacs from queen maculifrons insects, and the dose immediately preceding the untoward reaction was 1.5 sacs. Three months later, he tolerated without subjective or objective evidence of allergy, 6.4 sacs of the same antigen within a period of four hours. Table II will indicate that his conjunctival tolerance had risen tenfold.

As Figure 2 will indicate, a similar acquisition of immunity was exhibited by BAK. During his primary course in 1954, this man was tested (indicated by "t" on the graph) and then given his first therapeutic injection of 1.2 venom sacs extirpated from yellow jacket workers. There being no adverse effect on pulse or blood pressure, an additional four sacs were administered. He shortly complained of feeling hot, somewhat dizzy and "fuzzy" in vision and hearing. As after his serious

accidental sting, he sensed what he described as the weight of "an elephant sitting on my chest." There was slight nausea, perspiration and weakness, associated with an increase in pulse rate and a reduction in blood pressure. All manifestations disappeared shortly after his head had been lowered and epinephrine had been given intramuscularly. He was feeling normal within thirty minutes and in one hour accepted without event an injection of one venom sac. There was full tolerance of a subsequent dose of 0.4 sac. Two final injections totaling .88 sac led to momentary hypo-

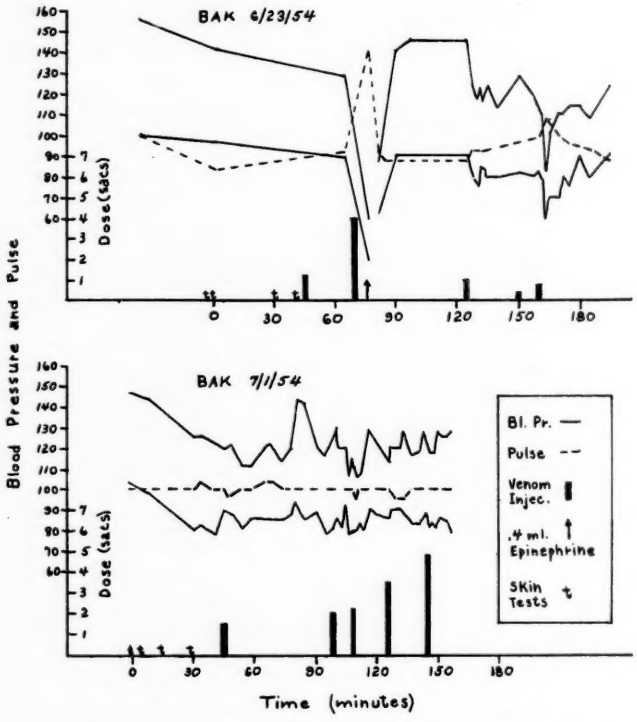

Fig. 2. Effect of venom on pulse and blood pressure of wasp-allergic patient during first and second visits.

tension and slight hunger pains as well as mild flushing, all of which disappeared spontaneously within ten minutes.

Eight days later the patient showed a sixfold increase in conjunctival resistance and a tenfold elevation of his cutaneous threshold. He tolerated completely the following amounts of venom from the same source as served for his earlier series: 0.6, 1.5, 2, 2.25, 3.5 and 4.8 sacs. In addition to all this, he submitted to the sting of a live honeybee without any systemic reaction.

TABLE IV. DOSAGE AND SYSTEMIC REACTIONS OF PATIENT, HOU, DURING FOUR VISITS IN 1953
(Yellow jacket venom)

Time (mins.)	Dose		Systemic Reaction	Dose		Systemic Reaction	Dose		Systemic Reaction	Dose		Systemic Reaction
	Sacs	Total		Sacs	Total		Sacs	Total		Sacs	Total	
	Visit of 6/8/53			Visit of 6/9/53			Visit of 8/23/53			Visit of 10/1/53		
0	0.1	0.1	none	4.0	4.0	none	0.2	0.2		0.2	0.2	none
30	0.9	1.0	none				2.0	2.2	none	(1.3*)		none
60	0.9	1.9	none	4.0	8.0	In 10 mins. itchy soles, palms, nausea, thready pulse, fullness of posterior pharynx, prostration.				10.0	10.2	none
90	2.25	4.15	none									
150	3.6	7.75	slight headache in 5 hrs.				2.0	4.2				
180							4.0	8.2	none			
240							Sting†		none			
300							(4.0 bald-faced)		none			

*Intracutaneous tests with venoms of bees and wasps other than yellow jackets.
†Yellow jacket worker.

The third overdose reaction was noted in HOU during 1953. Whereas she had tolerated a total dose of 7.75 sacs of queen maculifrons venom and gave no untoward response to an initial injection containing four sacs on the following morning, repetition of this dose in fifty minutes caused pruritus of the soles and palms within ten minutes, as well as mild nausea, a sense of fullness of the posterior pharynx and fleeting prostration. An acute drop in systolic and diastolic pressures as well as threadiness of the pulse were promptly remedied by intramuscular epinephrine. Two-and-one-half-months later, as Table IV indicates, she returned for a challenge test. At this time her threshold requirement with the intracutaneous test was found higher by tenfold. She tolerated without significant effect on pulse or blood pressure the following doses within a five hour period: two sacs of yellow jacket queen's venom; two sacs from jacket workers; then four of the latter; and finally a planned sting by a live yellow jacket worker. This was followed by the injection of four sacs procured from bald-faced hornet workers. Five weeks later she took in a single injection the contents of ten sacs removed from yellow jacket workers, with no untoward manifestations or circulatory effects.

ANTIGENIC RELATIONSHIPS AMONG THE VARIOUS HYMENOPTERA

A limited number of experiments were carried out with the intracutaneous and conjunctival procedures to determine the relative responsiveness of our wasp-allergic group to different hymenoptera venoms. Seven of their sera were also examined for skin-sensitizing qualities. Subsequently, two of the most potent specimens were employed for absorption with each of the several venoms so that cross-challenges could be made with the others in normal skin which had been prepared with the absorbed serum.

TABLE V. MINIMAL REACTIVE STRENGTHS OF VARIOUS HYMENOPTERA VENOMS IN WASP-ALLERGIC INDIVIDUALS
Examined by Intracutaneous, Conjunctival and Prausnitz-Kustner tests

Patient	Year	.01 ml Intracutaneously					.02 ml Instilled Onto Conjunctiva					.01 ml in Passively Sensitized Skin				
		Yellow Jacket	Paper Wasp	Bald-faced Hornet	Bumble-bee	Honey-bee	Yellow Jacket	Paper Wasp	Bald-faced Hornet	Bumble-bee	Honey-bee	Yellow Jacket	Paper Wasp	Bald-faced Hornet	Bumble-bee	Honey-bee
ARV	'53	0.001q*	0.5	0.01q			1.0q									
	'54	0.006	0.25		0.01		1.0	2.5				0.05		0.025	0.013	0.10
	'55	0.006	0.05			0.1	1.5	2.5			1.0					
BAK	'54	0.009	0.05	0.006		0.03	2.5		1.0			0.013	>0.006	0.002	0.003	0.10
														0.006q		
	'55	0.013	0.025	0.012			2.5	1.0								
FIE	'54	0.01		0.1			1.0		0.5			>0.025		0.006	0.05	1.0
HOU	'53	0.003q				0.1	0.67q		2.0q			0.10		0.006	0.05	0.075
												0.006q				
	'54	0.003	0.05				1.0	0.75			1.0					
	'55	0.006	0.05			0.025	1.0	1.0			0.2					
PER	'54	0.025					1.0					0.025		0.006	0.05	0.075
	'55	0.05	0.25			0.1	1.5	1.0								
SAU	'53	0.001q				0.05	0.57q				1.0	0.006	0.002	0.001	0.002	0.10
														0.003q		
	'54	0.006	0.025		0.006		0.5									
	'55	0.006	0.013		0.006	0.006	0.5	0.1			0.25					
WAL	'55	0.006	0.04			0.01	0.5	3.0			1.0					
BEC†	'54	0.5	0.5	0.01					1.5q							
				0.01q												
KRO	'54	0.05	0.025	0.01			1.0					0.025			0.025	0.037
		0.1q		0.01q												
NEL	'55	0.006					0.25									
WIL	'55	0.05	0.013	0.013			0.25	2.5	0.75							
GTH**	'55	0.5	0.1			0.1		1.5			0.2					
Range		.001 to .5	.013 to .5	.006 to .1	.006 to .01	.006 to 0.1	.2 to 2.5	.1 to 2.5	.5 to 2.0		.2 to 1.0	.006 to .1	.002 to >.006	.001 to .025	.002 to .05	.037 to 1
Median		0.01	0.05	0.01	0.006	0.06	1.0	1.0	1.0		0.6	0.025	0.004	0.005	0.013	0.1

*Queen insect (all other tests were done with workers).
**Paper wasp allergic (all other subjects were yellow jacket allergic).
†Clinically allergic to bald-faced hornet as well as to yellow jacket venom.

Although results with the direct tests of the skin and eye showed some tendency for individuals to be more reactive to the clinically important venom than to the others, during the passive sensitization studies the bald-faced hornet and bumblebee venoms appeared to be more active than the rest, as may be noted on Table V. This apparent inconsistency may rest on the limited sensitization studies done. In general the data for other hymenoptera resembled those for the yellow jacket as far as the tests of the skin and eye were concerned. They differed clearly from the results obtained with yellow jacket venom in normal subjects (see Table II). Only provisional conclusions should be drawn from these preliminary trials which represent the first attempt to explore the relationships among the hymenoptera venoms in the allergic patient by means of concurrent, controlled testing prior to immunization.

Cross-neutralization data were obtained with the highly active serum of SAU in two normal recipients on five different occasions and with the somewhat less potent serum of BAK on one. Replicate sites were injected with serum-venom mixtures for challenge in twenty-four hours with the homologous and the remaining venoms. Table VI summarizes the results by indicating the proportion of the total experiments which provided positive responses when challenges were made at twenty-four hours. Interpretation was always subject to control reactions evoked concurrently in sites sensitized with the plain SAU or BAK serum, correction being made for any nonspecific irritative responses in areas of unprepared skin or in sites prepared with the unrelated reaginic serum of KU, a ragweed-allergic subject. As indicated in the lower portion of the table, strengths could usually be located which would elicit specific responses in the SAU-sensitized site but which were without significant activity in the KU site.

It will be seen in the first row of Table VI that skin prepared with a wasp reaginic serum-yellow jacket mixture was unresponsive to this venom at twenty-four hours. Comparable sites challenged with .01 ml of bald-faced hornet venom, containing .006 sac/.1 ml, were similarly nonreactive in three of four experiments, the fourth trial providing a partial activation of the site. The outcome was similar when a duplicate area was challenged with venom of the paper wasp, two of three trials giving negative results. The bumblebee worker, however, apparently possessed different antigenic activity in its venom, since it provoked uniformly positive reactions of about half maximal size in skin which was no longer responsive to yellow jacket venom. Honeybee venom also appeared to contain activity different from that of yellow jacket venom, according to two of three experiments. Irritative qualities, however, made interpretation less certain than with the other venoms. These findings suggest that the venoms of the bald-faced hornet and the paper wasp possess only a small amount of allergen peculiar to themselves and lacking

TABLE VI. PASSIVE TRANSFER CROSS REACTIONS AMONG FIVE HYMENOPTERA VENOMS AFTER ABSORPTION WITH SERUM OF SAU OR BAK

(In Normal Subjects, MAT and CAD)

Proportion of Experiments giving Positive Response to Challenge

		Yellow Jacket Worker	Bald Faced Hornet Worker	Paper Wasp Worker	Bumblebee Worker	Honeybee Worker
Serum: Venom mixtures used to sensitise normal subject's skin	Yellow Jacket Worker	0/4 (self site)	1/4	1/3	3/3	2/3
	Bald Faced Hornet Worker	1/4	0/4 (self site)	0/2	4/4	2/4
	Paper Wasp Worker	0/2	1/2	0/2 (self site)	2/2	1/2
	Bumblebee Worker	3/4	3/4	1/2	0/4 (self site)	3/3
	Honeybee Worker	0/4	1/4	2/2	2/4	0/3 (self site)
Controls in CAD	SAU: saline KU: saline Normal skin	.025 = 2½ .025 = ± .025 = 1—	.006 = 2½ .006 = 1 pale	.006 = 3 .006 = ±pale .006 = ±red	.006 = 3 .006 = 1 pale .006 = 1 red	.1 = 2½ red .1 = 1½ pale .1 = 2 pale

in the venom of *v. maculifrons,* whereas their major activity depends on allergens present in the latter. Both the bees, on the other hand, exhibited important specificities in their venoms which were not possessed by the yellow jacket venom. When, instead of being employed as an absorbing agent, maculifrons venom was used as the challenging material, it evoked essentially negative responses in all areas except those prepared with bumblebee venom: serum mixture. These results, given in the first vertical column (headed "yellow jacket"), indicated that all the active constituents of *v. maculifrons* venom were present in the venoms of the paper wasp and the honeybee. In one of the four tests done in bald-faced hornet-prepared sites, a partial reaction indicated that a minor activity peculiar to yellow jacket and lacking in the bald-faced hornet venom was present in the former. The normal subject employed for this particular experiment was more highly responsive in general than was the one used for the other tests, and appeared to be able to pick up this small amount of activity. All but one of the challenges carried out with yellow jacket venom in sites neutralized for bumblebee venom provided good-sized, partial responses, giving evidence for absence in the bee venom of the major activity in the wasp venom. This indicated that the two venoms had much less in common than was the case for the rest of the hymenoptera.

When bald-faced hornet venom was selected for absorption of the serum, subsequent challenge with yellow jacket venom provided negative responses with the single exception which has just been mentioned. As indicated in row 2, polistes venom likewise prove ineffectual. Thus there must exist in neither of the challenging materials any important allergen

which is not also possessed by the hornet venom. The corresponding cross-test with the bumblebee's product, however, provided partial reactions in all trials while the honeybee challenge afforded such responses in half the tests. Both these bee venoms must have contained important activities which were lacking in the hornet allergen. When the latter was employed as the challenging agent, results as shown in the second horizontal column again indicated the similarity of the venom of the hornet to those of the paper wasp, yellow jacket and honeybee which forestalled its reaction in most trials. The one positive response in a yellow jacket neutralized site and in the polistes and honeybee prepared areas probably indicated the existence of a minor activity which was peculiar to the bald-faced hornet. Three of the four trials with the latter's venom in sites prepared with bumblebee venom mixture provided good-sized reactions, showing that the bumblebee product lacked some activity important to the allergenicity of the hornet. In this respect, the bumblebee distinguished itself from the other hymenoptera tested.

Serum absorbed with paper wasp venom was unable to sensitize normal skin toward yellow jacket venom and did so only partially for bald-faced hornet venom in one of two trials, as indicated in row 3. The major activity of these two venoms, therefore, depended on specificities possessed by the paper wasp venom, strengthening the evidence given by the above experiments that the three wasps had much in common allergenically. Both the bumblebee and the honeybee venoms, however, must have had extra antigens since they both evoked positive responses of fairly large size when used as challenging agents. This again set them apart from the three wasps. The data given in vertical column 3 indicated that paper wasp venom contained no activity which was not also present in bald-faced hornet venom, the latter completely inactivating the site for the challenge test. There must have been a small amount of individualized activity in paper wasp venom which is lacking in yellow jacket venom, since the more responsive test subject gave a partial response to the polistes challenge. The cross-test reaction evoked in the bumblebee venom site was quite large in one test but negative in another. Presumably a certain amount of antigen present in paper wasp venom is lacking in the bee. Both reactions to paper wasp venom in honeybee absorbed sites were rather large, indicating that honeybee venom lacked a major activity possessed by the wasp. Thus paper wasp venom appeared to be more complex or different in specificity than either of the bee venoms, whereas it was in general similar to the two other wasps.

Row 4 indicates that bumblebee venom used as an absorbing agent was unable to negate the cross-test reactions of the three wasp venoms. The latter evoked good-sized reactions in most trials. The same was true for the challenge with honeybee venom, indicating that bumblebee venom is lacking in important activities possessed by all the other hymenoptera. The distinct nature of the bumblebee allergens was again revealed when the venom was

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used as the challenging agent. Vertical column 4 shows that positive responses were obtained in all sites absorbed with the three wasp venoms. The reactions were of good size, indicating that the bumblebee possessed an important activity which was lacking in wasp venoms. In sites receiving honeybee absorbed serum, on the other hand, only half the tries gave positive results and only one of the responses was more than suggestive. One concludes that the bumblebee venom possesses some minor activity which is lacking in the honeybee product, whereas its major activity rests on a common component.

The final series of cross-tests was carried out with honeybee venom. Horizontal row 5 reveals that this venom completely inactivated the sensitizing serum toward retest with yellow jacket venom and, with one minor exception, did the same thing for the bald-faced hornet venom. By the way of contrast, paper wasp venom was able to evoke reactions of considerable size in both its challenges of honeybee-prepared areas, indicating that it possessed an important activity which was lacking in honeybee venom. As mentioned before, the challenge of a similar site with bumblebee venom provided a significantly positive response in only one instance. The results given in vertical column 5 reveal that honeybee venom, used as a challenging material, evoked good-sized responses in areas neutralized against yellow jacket venom on two of three occasions and similar reactions in sites containing hornet venom-absorbed serum. While the corresponding test of a paper wasp prepared area gave a sizeable response in one instance, the other test gave a negative result. One concludes that honeybee venom contains certain rather important activities which are lacking in the three wasp venoms. Large, but submaximal, reactions developed when honeybee venom was injected into a bumblebee-absorbed area, indicating that it possessed definite activity which was lacking in the bumblebee venom.

In general these results, which are preliminary, impress one with the idea that the three wasp venoms have a great deal in common while at the same time each possesses a minor activity which is peculiar to itself. The honeybee, on the other hand, appears to be about as closely related to the wasps as it is to the bumblebee in that its venom contains the allergens responsible for the activity of yellow jacket venom and probably for most, or all, the activity of the hornet's venom. It lacks, however, important activities associated with paper wasp venom. Honeybee venom appears to possess most of the important activity of bumblebee venom, as shown by its capacity to inactivate most of the challenging power of the latter. On the other hand, it possesses other active constituents which the bumblebee lacks, as revealed by its activity in bumblebee venom-serum prepared skin. Since, however, the honeybee venom tended to be irritating to skin prepared with the unrelated reagins of KU, results were subject to some question. This doubt did not apply to bumblebee venom, which differed distinctly from all three wasp venoms as shown by positive

reactions in all reciprocal tests. Inasmuch as these responses were not maximal, it was evident that some common allergens also existed in the two sets of venom.

DISCUSSION

If the preliminary results with SAU and BAK sera can be confirmed with other specimens, one could deduce that an individual sensitized by the yellow jacket would also be susceptible to the sting of the bald-faced hornet as well as to polistes venom, since both appeared capable of obliterating the challenge responses to yellow jacket allergen. The same situation was encountered for the honeybee, which carried in its venom all the activities characterizing the yellow jacket plus additional ones peculiar to itself. Important activity in the bumblebee venom, on the other hand, appears to be unrelated to any of the other venoms except the honeybee's. It would not be anticipated, therefore, that the yellow jacket-sensitized patient would be comparably or invariably susceptible to bumblebees. One would surmise, however, that the honeybee-allergic patient would be adversely affected by the bumblebee, since the honeybee's venom was capable of forestalling, at least partially, the challenge activity of the bumblebee venom.

There are several indications that all the venoms contained some antigen in common. For one thing, the cross-absorption studies have revealed that each venom is capable of curtailing to a certain extent the responses of all the others during challenge tests. Furthermore, each of the seven sera examined in normal skin by the conventional Prausnitz-Küstner technique was found to possess reagins for all the hymenoptera venoms tested, in spite of the fact that the donors of the blood gave histories of allergic episodes after yellow jacket stings (HOU also having collapsed from a honeybee sting). Finally, not one of the thirteen patients examined by the intracutaneous and conjunctival methods failed to respond to any of the five venoms, a situation which might well rest on the existence of common activities in all, provided their histories of accidental stingings are reliable.

The cross-test data suggest that not only common but type-specific allergens, peculiar to the individual hymenoptera, are involved. The bumblebee venom appears in particular to contain highly active, individualized components. One is forced to speculate in view of this situation as to whether the donors, SAU and BAK, had not at some time in the past received a forgotten bumblebee sting which produced sensitizing antibodies for this bumblebee activity. Both sera were procured prior to the stings listed on Table II. Both specimens were unusually reactive with bumblebee venom according to the data given for them and the other sera in Table V.

At the present stage of our knowledge, it is important for the physician to learn the exact identity of the offending wasp or bee since immuniza-

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tion with another type might provide the patient with protection against the common allergen but fail to do so against the type-specific variety. Although one might consider avoiding this risk by using a mixture of the several hymenoptera venoms, this carries the theoretical danger of induced sensitization for the nonetiologic varieties. Since venom hypersensitivity seems to be a more or less normal response of man to the parenteral introduction of foreign protein and resembles in a number of ways serum disease, drug idiosyncrasy and experimental anaphylaxis, it would seem essential to avoid the parenteral use of venom whenever possible. This makes it encumbent on the physician to establish as accurately as he can the identity of the offending insect. A knowledge of the haunts and habitats of different members of the order will often settle the problem in instances where the patient is unable to describe the insect but knows the circumstances under which he was stung. A few screening tests with yellow jacket venom by the intracutaneous and conjunctival methods should serve, with reference to Table I and II, to place the patient in the normal or hypersensitive category. If he falls in the former class, it is unlikely that he is allergic to any of the hymenoptera studied by us since Table V indicates that the levels of reactivity are of a comparable order. If the screening tests point to hypersensitivity, one should extend the tests to other likely members of the species in order to locate the most active venom. In this way one would increase the probability of selecting the correct venom for use in immunization.

If, after the foregoing efforts, the physician is still uncertain which individual member of the order was involved, he is justified in immunizing with any of the wasps on the ground of their demonstrated overlapping allergenicity. Our experience would lead us to suggest yellow jacket venom as the antigen of choice, since it possesses activity in common with the two other wasps, with the honeybee and to a lesser extent with the bumblebee. (Furthermore, the yellow jacket is responsible for the majority of stinging accidents among individuals other than beekeepers.) Support for the assumption that yellow jacket venom confers cross-protection may be found in Table II, which shows that three maculifrons-immunized subjects tolerated fully the stings of honeybees, bumblebees and an unidentified wasp (polistes?).

Although three marked overdose reactions were encountered during the early experimental period of venom therapy, when neither the tolerance of the patient for injected antigen nor the minimal protective doses had been established, these were entirely avoided during the third year when a more standardized schedule was followed. Detailed description was given of these reactions inasmuch as an understanding of the syndrome should prove valuable to the physician who has been called upon to treat a patient in the throes of a sting reaction or to immunize highly susceptible subjects against venom. These reactions in general

resembled histamine responses in that they were characterized by flushing, headache, dizziness, nausea, sweating, tachycardia, acute hypotension and, in one instance, hunger pains, in addition to localized urticaria. Epinephrine 1 :1000 given into the muscle in a volume of 0.25 ml invariably reversed all manifestations. It might be expected that parenteral antihistamines would also be effective. The syndrome is probably analagous to acute reactions following the injection of penicillin, foreign serum, hormones, et cetera. Their severity should inspire every physician to take all precautions against their development.

The wasp-allergic patient can be given considerable assurance regarding the success and safety of his immunization, especially if he is able to identify the provocative insect. Acquired immunity has been demonstrated according to several criteria. One of these is the patient's acquired capacity to tolerate amounts of venom which were originally provocative of marked overdose reactions. Most convincing is his ability to undergo planned and accidental stinging without untoward effect following a course of therapy. Heightened thresholds of cutaneous and conjunctival responsiveness to venom are also indicative of resistance. Experience in 1955 has shown that a total of about six sacs of venom is protective against the sting of the homologous wasp. Since such a course can be completed during a single visit of some hours without untoward reaction, there is every reason to anticipate that the injections could be stretched out over one or two months with equal effectiveness and safety. The single visit was chosen by us because it was more convenient for patients who came from distant areas. It also enabled us, during the experimental period, to determine the limits of tolerance of each individual for administered venom during several hours of intermittent injection. The extent to which this limit was raised subsequent to treatment then served to assure us that the patient had acquired immunity.

Although no titrations were attempted, it is logical to assume that immunization is accompanied and perhaps conferred by the formation of blocking antibody similar to that acquired by the pollen-[3] or insulin-allergic[4] subject following injections with the related antigen. The elevation of the thresholds of response in the skin and eye of the venom treated subject is presumably dependent on their acquisition of this type of antibody.[5]

The use of the venom sac as the unit of measurement of wasp allergen is a temporary expedient, pending an arrangement for the speedy removal of sufficient venom to permit chemical assay on each batch. The adoption of a chemical standard should increase the reproducibility of diagnostic tests and therapeutic results.

Carried out with specific antigen and with all precautions, the prophylactic management of wasp allergy is undoubtedly a life-saving measure to which the highly sensitized individual is entitled.

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CONCLUSIONS

1. Venom removed from the extirpated sacs of live wasps has been employed for the first time for the diagnosis and immunization of wasp-allergic individuals.

2. The levels of response of normal young adults to the venom of the yellow jacket wasp have been delineated for the first time, by means of concurrent tests of the skin and eye as well as a three-minute sting with a live worker insect.

3. During comparable tests of the tissues of wasp-allergic subjects, it was found that lower concentrations of venom sufficed for their threshold responses. Following immunization with the venom of the yellow jacket, however, the patients' intracutaneous and conjunctival reactions approached those of the normal, control subjects. Responses of immunized patients to deliberate insect stings also resembled those of the control group.

4. Not only the direct tests of sensitized individuals, but also experiments with their serum in normal skin, indicated that five of the hymenoptera (yellow jacket, bald-faced hornet, paper wasp, honeybee and bumblebee) possess a common allergenic specificity, while each also contains in its venom a component which is peculiar to it. The honeybee appears to be more closely related to the three wasps examined than is the bumblebee, and the three wasps have a great deal in common. Probably each venom is a complex antigenic mixture.

5. Three "anaphylactic" syndromes encountered during early trials with venom immunization resembled the acute hypotensive reactions to histamine.

6. Wasp venom appears to be a highly satisfactory immunizing agent against wasp sting reactions as judged by several criteria, including deliberate and accidental stings. A total of as few as six venom sacs appeared to be sufficient for protection and could be administered during a single, prolonged visit without untoward effect.

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ALLERGY TO CASTOR BEAN MEAL

Report of a Case of Anaphylactic Shock and Gastrointestinal Hemorrhages

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ALLERGIC reaction to the products of castor bean is not new. As far back as 1923 Bernton[1] reported a case of asthma in a man working with castor beans in a laboratory, and he proved sensitivity. In 1928, Figley and Elrod[2] demonstrated a high grade of sensitivity to an extract of castor bean dust in thirty of thirty-two asthmatic patients living in close proximity to a castor oil factory. Vaughn[3] reported three cases of sensitivity to castor bean pomace on exposure to this product used in fertilizer. Arnold[4] has described poisoning from castor bean, and Robbins[5] reported a case of super-sensitiveness to the poisonous action of the castor bean. Snell,[6] Follweiler and Haley,[7] Bennett and Schwartz,[8] Ratner and Gruehl,[9] and Barnard [10] have contributed to the literature on castor bean sensitivity.

Small,[11] in 1952, reported nine cases of asthma and two of hay fever as a result of inhaling castor bean pomace. He reports a tenfold increase in the production of castor bean pomace in Southern California with an anticipated fourfold increase. It was suggested because of the increase in production and extreme toxicity of castor bean meal, which is being used more extensively in fertilizers, that proper labeling be mandatory. Because castor bean meal has a relatively high nitrogen content and is far cheaper than competitive products, such as cotton seed meal, its commercial attractiveness is increasing. (The total nitrogen analysis on ground castor bean approximates 33.7 mg per grain or 3.37 per cent.) There is an increasing demand for castor oil and its fractions because of its industrial uses in paints, varnishes, lacquers, plastics, rayon, nylon, rubber textiles, asphalt tile, cosmetics, ink, electrical insulation, fungicides, leather products and soaps. The Armed Services also use castor oil in recoil mechanisms, jet engines, brake fluids, explosives and greases. Prior to 1949 there were less than 100 acres in cultivated castor beans, but it is estimated that the present acreage is in excess of 200,000.

We have seen allergic symptoms and clinical sensitivity, confirmed by skin test in farmers and their families in the Imperial Valley, workers in warehouses where grains and castor beans are stored, and in truck drivers who transport the castor bean and its products for distribution. Such sensitivity is becoming more common. A report of a case of marked sensitivity follows.

CASE REPORT

A thirty-nine-year-old milk truck driver, who had recently developed a chronic cough following exposure to soil around his house, where he had moved shortly before, stated that when he gardened he had more difficulty, and that when his neighbors fertilized, he had a severe cough associated with wheezing. In view

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of this history, it was suspected that some of his neighbors might be using castor bean meal which is increasing in popularity as a fertilizer in the San Diego area. The patient was given a scratch test to an extract of this material, which resulted in an equivocal reaction. Although a 1:10 000 dilution is recommended and has been used in the past for intradermal testing, since we knew this extract to be a highly potent antigen, a four times weaker solution was prepared (1:40,000), and a minute amount of the material was injected intradermally. (This represented less than one drop of a solution which at first was diluted tenfold and subsequently an additional fourfold.)

Within ten seconds the patient turned grey and vomited. Within one minute he vomited again, this time some small flecks of blood were present in the vomitus. Immediately therafter, he leaned against the wall, his face became grey-blue, and this 210-pound-man slid to the floor in a cold, clammy sweat. It took three persons to get him into position for immediate administration of adrenalin, intravenous Benadryl® and aminophyllin, oxygen, artificial respiration, and intramuscular Neosynephrine® to sustain his blood pressure, which was unobtainable. Within the next twenty-five minutes, during which time the patient remained comatose, the pulse was thready and occasionally disappeared and he was continually supervised by doctors and nurses. One doctor gave oxygen and artificial respiration, another intravenous and intramuscular medications, and another checked blood pressure, pulse, et cetera. One nurse was kept busy attempting to keep the patient warm with hot water bottles, blankets and massage. Another nurse was running errands and wringing her hands, and a third nurse was trying to calm the patient's pregnant wife, who was at term, so that it would not be necessary to do a delivery during this crucial period. At the same time she was trying to answer the six-year-old son's question: "Is my daddy going to die?" The answer seemed to be "Yes." In about forty-five minutes, the patient's blood pressure had risen to 20/0, and he had opened his eyes. He was diffusely swollen with generalized angioedema, and had a thick tongue and hoarseness, and was slightly cyanotic. He passed a copious stool, without blood present, and then three more stools, all containing increasing amounts of blood.

As soon as possible, the patient was taken to the hospital in an ambulance and was given two pints of blood very rapidly by the forced venous route, and the blood pressure gradually arose to 80/40. He was maintained on adrenalin, two subsequent transfusions, ACTH, and additional supportive measures. A surgeon was asked to see the patient because of a presumptive ulcer history. The patient continued to bleed for forty-eight hours, in lessening amounts, and soon recovered sufficiently to take oral liquids. However, when he began to take milk, he developed cramping, gas and loose stool, associated with wheezing. On skin testing to cow's milk, in spite of the fact that I promised myself to do no more testing on this man, he was found to be highly sensitive, and when this was eliminated from the diet, he got along well. (No ulcer was ever demonstrated in this patient by subsequent studies.) He did well on goat's milk, which was available to him on his milk route, and when he tried cow's milk on several occasions, he again developed symptoms of gastroduodenitis, as well as asthma, and on two of these occasions had bloody stools. Because of continued asthma at home, and because he went into acute status asthmaticus, with unconsciousness and shock, when in a neighbor's house where there was an unopened sack of castor bean meal in the garage, we advised that he return to Washington State, his former home, where castor bean meal is not yet in common use as a fertilizer. A letter received a few weeks ago tells us that he is in good health and that he has had no further respiratory or gastrointestinal allergic symptoms.

DISCUSSION

This case is noteworthy from several aspects. The near death from the intradermal injection of a very weak solution of allergenic extract in the smallest possible amount is in itself striking. The ability to develop status asthmaticus and shock where the offending inhalant is in a closed container as far away as the garage is most unusual.

This patient also demonstrates the possibility of gastroenteritis, with gastrointestinal bleeding, due to the ingestion of an allergen. In this case the offending food was cow's milk.

In retrospect, it is probably inadvisable under any conditions to use an extract of castor bean meal for intradermal testing. Inhalation of this allergen under controlled conditions to obtain scientific proof of the correlation between skin reaction and clinical sensitivity should certainly never be attempted with this substance. In the event of a negative scratch reaction, consideration should be given to a combination scratch-patch reaction. The punch test should probably be used initially. Puncture test consists of scarifying the skin once with a sharply ground double point of the partially cut-off eye of a sewing needle, which has been dipped into the solution of antigen.

SUMMARY

1. The importance of castor bean meal (pomace) as an increasingly significant allergen is reported. Its extreme potency is noted.

2. A near death from intradermal testing to a small amount of a very weak dilution of extract is recorded.

3. Gastrointestinal hemorrhage during anaphylactic shock and subsequent gastrointestinal bleeding due to ingestion of a common food (milk) is described.

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A PARADOXICAL REACTION FOLLOWING THE ADMINISTRATION OF LAKED, INCUBATED, AUTOGENOUS BLOOD

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IN the writer's experience, certain blood preparations provoke a more intense reaction in allergic subjects when given in very high, rather than low, dilutions. To eliminate the element of chance, these tests were repeated over and over again. The present study, which began more than twenty years ago, includes a large number of allergic patients, with non-allergic subjects as controls.

METHOD

Freshly drawn blood was laked under sterile conditions by adding 0.5 ml of blood to 9.5 ml of triple distilled water. The mixture was agitated vigorously and incubated at a temperature of 103° to 104° F, for twenty to thirty hours, as described by Rogers[2]; it was then kept under refrigeration. Cultures were taken of all blood preparations before they were administered to the patients, and, of course, all contaminated blood was discarded.

When 0.1 ml of this preparation was thoroughly shaken with 0.9 ml of physiologic saline solution and reinjected subcutaneously into the same allergic individual with active symptoms, the recipient usually showed no perceptible reaction except, perhaps, some slight local tenderness.

EFFECT OF VERY SMALL DOSES ON ALLERGIC PATIENTS

When the above preparation of laked, incubated blood was diluted through 1 to 10 dilutions in triple-distilled water, each vigorously shaken and the last dilution prepared in saline, finally making a 10,000 or 100,000 in saline, and 1.0 ml of either dilution was injected subcutaneously into the actively allergic subject from whom the blood had been taken, there usually followed a marked exacerbation of the allergic symptoms. In all, 732 allergic patients were tested in this way; the distribution of the patients and the results obtained are shown in Table I.

Each of the patients in this series received from four to five injections of the blood preparation at weekly intervals.

The results, which were quite consistent, showed that 83 per cent of all the allergic patients so treated reacted with considerable intensity when injected with the highly diluted preparation. Ninety-one per cent of the same group showed no reaction whatever when injected with the undiluted preparation, while the remaining 9 per cent showed only a

Dr. Lipton is an Associate Fellow of The American College of Allergists.

TABLE I. EFFECT OF ADMINISTRATION OF LAKED, INCUBATED BLOOD IN DILUTIONS OF 1:10,000 OR 1:100,000 TO ALLERGIC PATIENTS

Type of Allergy	Number of Patients	Known Etiology No. of Cases	Unknown Etiology No. of Cases	Symptoms Aggravated by Undiluted Blood	Symptoms Aggravated by 1/10,000 or 1/100,000 Diluted Blood
Asthma	358	219		19 (9%)	166 (76%)
			139	11 (8%)	108 (78%)
Vasomotor rhinitis	254	115		11 (10%)	85 (74%)
			139	13 (10%)	100 (72%)
Chronic urticaria	72	21		2 (10%)	18 (90%)
			51	5 (10%)	44 (86%)
Eczema	37	17		1 (6%)	16 (94%)
			20	1 (5%)	19 (95%)
Nonallergic controls	85			5 (6%)	5 (6%)

Note: Known etiology refers to patients in whom tests with antigens disclosed the cause of the allergic condition. Unknown etiology refers to cases where tests failed to show the cause of the allergy.

mild reaction. Therefore, these experiments demonstrate quite clearly that allergic patients react with greater intensity to the higher dilutions of autogenous, laked, incubated blood than to the lesser dilutions.

The general reactions observed with laked, incubated blood are akin to the negative phase reactions of Wright, as cited in Zinsser.[3] They manifest themselves as either focal or general reactions or a combination of the two. Focal reactions following the administration of the blood preparation have not been observed among my patients. The focal reactions manifest themselves in the form of temporary exacerbation of the presenting allergic symptoms. The general reactions are characterized by malaise, fever, polyuria, gastrointestinal and menstrual disturbances, differing considerably from the constitutional changes seen with other allergic preparations. Anaphylactic reactions have never been observed. The latter reactions often present themselves as a recurrence of old complaints appearing in the reverse order to that in which they first developed. In addition, quiescent foci of infection may sometimes become activated; for example, a chronic sinusitis may turn acute. Occasionally, a patient may show temporary improvement of his condition. The general reactions are of no serious import and are short lived.

Despite the innocuousness of the blood preparation, it should be used with great caution in tuberculous patients, in whom the possibility exists of a flare-up of a quiescent lesion. Similarly, it should not be used in the critically ill patient where a reaction of any kind may prove disastrous.

EXPERIMENTS WITH NORMAL CONTROLS

Eighty-five nonallergic patients, varying in age between ten and fifty-eight years, were used as controls. Each patient received three or four injections of autogenous, laked, incubated blood preparations of the same

concentration and dilution as that used in the allergic patients. The results of these tests may be summed up by saying that eighty (94 per cent) of these patients did not react in any way to either the concentrated or diluted antigen. The remaining 6 per cent of the patients complained of general body aches lasting for several days and subsiding spontaneously. These symptoms were apparent following administration of both the concentrated and dilute form of the blood preparation.

In another series of experiments, the same nonallergic patients were injected with heterogenous blood preparations derived from patients with asthma, vasomotor rhinitis, chronic urticaria and eczema. Each control received four injections at weekly intervals. No reaction was seen to follow either the concentrated or highly diluted blood preparation in 94 per cent of the cases. We conclude, therefore, that the reactions observed following the administration of diluted, laked, incubated blood are applicable only to allergic individuals; they rarely occur in nonallergic people.

ADDITIONAL EXPERIMENTS

Additional experiments were made with: (1) laked, non-incubated blood; (2) incubated, non-laked blood; and (3) non-laked and non-incubated blood. In these studies, 700 of the 721 patients tested in the previous experiments were used. Each patient received four or five injections of the blood preparation at weekly intervals. These preparations were as free of focal reactivity as was laked, incubated blood. Focal and general reactions, however, were absent in 630 (90 per cent) of the patients, regardless of whether the blood preparations were administered in high or low dilutions. The remaining 10 per cent complained of temporary aches and pains all over the body. It is quite obvious, therefore, that the paradoxical reaction observed in the first series of experiments with laked, incubated blood could not be obtained if the blood is prepared in some other way.

In another series of experiments, 620 allergically active patients received laked, incubated, heterogenous blood preparations. In these studies, as in the previous ones, the patients did not react to either the low or high dilution of the antigen in 94 per cent of the cases, indicating that the blood injected must be autogenous in order to produce the effective reaction.

COMMENT

These experiments demonstrate that laked, incubated, autogenous blood is capable of provoking more reaction when administered to allergic individuals with active symptoms in high dilutions than when given in a more concentrated form. It has also been observed that to be effective, the blood used in the preparation must be autogenous, laked, and incubated.

If prepared in any other way, or if administered to nonallergic subjects, the blood preparation is without effect.

A perusal of the literature does not seem to disclose parallel observations. Remotely similar findings, however, could be discerned in Hansel's[1] work with optimum doses of staphylococcus toxoid, pathogenic molds, pollens, and dust.

At the present state of our knowledge no explanation can be offered for this paradoxical reaction, and the entire problem is left open for further investigation.

SUMMARY

A paradoxical reaction has been described in which autogenous, laked, incubated blood preparations were effective in producing focal and general symptoms when administered in high dilutions to allergic patients, while low dilutions did not give such an effect. Non-autogenous, non-laked, non-incubated blood and non-laked and non-incubated blood is without effect.

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Submitted February 13, 1956

GEL DIFFUSION TECHNIQUES

Gel diffusion techniques for the study of antigens and antibodies have been used with increasing frequency in recent years. They allow one to determine the relative concentrations of individual antigens and antibodies in complex mixtures. In the technique of simple gel diffusion studied extensively by Oudin, the antiserum is mixed with agar in the bottom of a small tube, and the antigens are layered on top. Each antigen-antibody system forms a band of precipitate which migrates into the agar. Since the rate of migration is dependent on the coefficient of diffusion of the antigen and on the relative concentrations of antigen and antibody, and since these factors are rarely the same for different systems, each band of precipitation can usually be distinguished by its characteristic rate of migration. The quantitative aspects have been studied by various workers, and it is possible to estimate antigen diffusion coefficients and relative quantities of antigen and antibody.—JOHN R. PREER, JR: A Quantitative Study of a Technique of Double Diffusion in Agar. From the Zoological Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania.)

PRESIDENTIAL ADDRESS

LAWRENCE J. HALPIN, M.D., F.A.C.A.

Cedar Rapids, Iowa

THE notes on the care and management of every patient are charted by the physician on the clinical record. A review of that record should reveal the changes that have occurred and suggest recommendations for future reference. However, the patient who is of current mutual interest is a healthy one. It is our American College of Allergists, whose progress has been observed by all of us and whose future management is the concern of each individual member. I shall attempt in this "state of the union" message to review the events of the past year and to submit certain suggestions for your perusal and consideration in the months to come.

The many benefits you receive as a member of The American College of Allergists are positive reflections of the enthusiastic and untiring application of your efforts for the continued improvement of your society. It has been a source of personal gratification to me to have talked and corresponded with many of you during my term of office. From these contacts, the officers and regents of your College have been apprised of your thoughts and ideas. It is your responsibility as a member to preserve the democratic standards which govern the College. We are proud of this code of conduct which is regarded as unusual in medical circles. The affairs of your College are managed by your elected representatives. If your status is that of an active member, you must have the drive and determination to acquire election to Fellowship. If you are a Fellow, you hold the future of this College close to your heart. It is by your counsel, suggestions and loyal cooperation that your elected representatives become keenly cognizant of your welfare.

The primary duty of the president of the College is to serve as chairman of the Board of Regents. This governing body consists of ten elected members who meet in two executive sessions at the time of the annual meeting. On these occasions, important College affairs are decided, College business is transacted, and foundations for future accomplishments are planned.

The president is also a member of the Board of Directors, a group of five officers who, at an interim meeting, undertake the management of such College business as requires immediate and active attention. The Board of Directors presents suggestions to the Board of Regents for their consideration, study and decision. The immediate past-president becomes the chairman of the Board of Directors. The President has been, therefore, the only liaison officer between these two important bodies. This week, the membership of the Board of Directors was increased to

Presented at the Twelfth Annual Meeting of The American College of Allergists, April 19, 1956, New York, N. Y.

include a representative from the Board of Regents to be chosen by the Board of Regents from those members who are serving the second year of their three year terms. This increase effects a closer liaison between the Boards of Regents and Directors.

The members of the Board of Regents are not relieved of College responsibilities in the interval between their annual meetings. Frequent correspondence from the executive office requires their time, thought, and opinion. Instituted this year were periodic letters by which each member of the Board is kept aware of any presidential opinion or action. These letters are in fact summaries of all correspondence pertaining to College affairs. No action is taken by any officer without the approval or sanction of this governing body. You are to be complimented upon the wisdom with which you have chosen your regents and directors. My association with these gentlemen in this past year has been a source of satisfaction to me, and I thank you for giving me the opportunity of working with them.

At the last annual meeting the College was informed by Doctor Fred W. Wittich of his desire to relinquish his office and to effect his retirement as of December 31, 1955. Words alone can never serve as an adequate expression of the debt this College owes to this founder. As a parent loves the child, so has Doctor Wittich loved the College. His efforts and labors in behalf of the College have been unselfish, untiring and unceasing. He would be the first to admit that every moment has been pleasant and worth while. We, who have been closely associated with Doctor Wittich, have always been acutely aware of the time and consideration he has given to College affairs. If each of you had had the privilege to know him intimately, you would appraise and appreciate him as we do.

You, the Fellows and members of the College, should know that the Board of Regents has given tangible recognition to Doctor Wittich's unselfish efforts in our behalf. When his intention to retire was realized, the Board of Regents appointed a committee to effectuate a plan to give meaningful expression of our gratitude. This committee, with Doctor Hugh Kuhn as chairman, after thoughtful and prolonged study, successfully resolved many questions which will result in equitable retirement compensation for this distinguished founder. His present capacity is that of general consultant. As a result, Doctor Wittich's desires were respected; and his retirement was effected at the close of 1955. I feel certain that he is contented and happy in his—and I quote—"old age and pasture." His letters to the officers have confirmed those beliefs.

The College is exceptionally fortunate to have the capable services of Mr. Eloi Bauers, our executive vice president and counsel. He has carried out the responsibilities of his own appointive office and has shouldered the burdens of the additional duties required of an interim secretary. For the past few years Mr. Bauers has made arrangements for the annual

meetings, the many details of which are prolonged and exacting. He has managed the executive offices since January 1, 1956, and has been most liberal to each committee and each officer with his time and his assistance. Mr. Bauers' report to you is only an indication of the interest and concern he has applied.

The responsibilities of such an office are demanding, varied and numerous and can be successfully accomplished only by a full-time executive officer. However, the elected officer, who is a practicing allergist, cannot devote the time required to this exacting position. The College must have a permanent home from which all administrative procedures can be accomplished. The Regents have had and will continue to have this question on their agenda until the proper solution is resolved.

And now for the American Foundation for Allergic Diseases. It was established through the joint efforts and support of The American College of Allergists and The American Academy of Allergy. During the next two to three years this active and progressive foundation will concentrate its efforts upon three focal areas—research, medical training, and public education. A seven-point program of basic research has been recommended by the Scientific and Educational Council. This program is briefly tabulated as follows:

1. How the cells of the body are affected by antigen-antibody reactions.
2. How to prevent antibody formation.
3. Histamine metabolism.
4. The enzymes.
5. Autosensitization.
6. The collagen diseases.
7. Psycho-physiological factors.

Post-doctoral research fellowships will be offered to qualified physicians whose projects lie within one or more of these seven areas. The Foundation's ultimate desire is to actuate eighteen or more research projects within the next three years.

A comprehensive program of fellowships, scholarships and residencies has been adopted by the Foundation. This should stimulate interest in the study of allergic diseases and provide an incentive for capable young physicians to enter this expanding branch of medicine.

The public education program of the Foundation will continue the preparation and distribution of information on allergic diseases. To my mind, this is one of the really important tasks to which the Foundation must unceasingly give special and vigorous attention. The cost of these goals has been estimated by the Foundation to be in excess of $1,000,000 for a three-year period. You must play an active part in providing this necessary sum. Your contribution may be large or small, but I assure you it will be welcome and will be wisely utilized.

Further evidence of the strides that allergy has made is the designation

of The National Institute of Allergy and Infectious Diseases. The institute was formerly known as The National Microbiological Institute. This important branch of the United States Public Health Service is worthy of your interest and your intellectual support.

And now, as regards amalgamation with The American Academy of Allergy: In 1955, we adopted a resolution which directed a committee to study the possibilities of such amalgamation. The members of this committee are capable men who have given freely of their time. They have met with a similar group appointed by the executive committee of the Academy. There are some points upon which the College and Academy representatives were in complete agreement. There are other features of this undertaking which, at first glance, would seem to be insurmountable. Time and further study are required to bring all of the necessary steps into proper focus and alignment.

What are the advantages of a single allergy society? It will be recognized by every physician that the multiplicity of medical meetings demands additional enforced absence from office practice. There is a noticeable duplication of membership in the two organizations, and amalgamation would seem to be advantageous to this minority. For those physicians who hold membership or Fellowship in each society, the financial saving offered by single dues would be an enticing lure. Considerable economy would result from having a single administrative force. Program chairmen would find it an easier task to arrange only one scientific session each year. The editor of a single official publication would have a wider selection of papers from which to choose. A single allergy society may appear to be strong evidence of complete agreement and unity, which strength would reflect itself in the support of other necessary objectives.

There are a number of projects in which the College and the Academy are already closely allied. As a consequence, both societies have benefited from these alliances to emerge with a stimulating spirit of friendliness and cooperation. The major goals we have gained and the paths we have followed have been essentially parallel through the years. It is significant and complimentary to both the Fellows of the College and the Academy that their combined efforts have finally resulted in so much unity of opinion and purpose.

Now let us look at the other side of the ledger. The American College of Allergists has gained its rightful place in organized medicine. This has been accomplished by the rigid application of the principles upon which the College was founded. Because of your excellent efforts in the instructional courses, research has been encouraged and clinical allergy has become recognized as an important part of the practice of medicine. An allergist cannot be created by a few days of postgraduate instruction, but interest and understanding can be developed to permit a better appreciation for sound measures of diagnosis and treatment.

We should not underestimate the fact that there is a healthy com-

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petitive force when two parallel groups are active. One reason for College progress has been the Academy, just as the College has been a strong motivating force in Academy success. This spirit has been friendly, cooperative and stimulating for each group. The dissolution of this competition would be detrimental to ourselves and to allergy as a specialty. Were amalgamation to be accomplished, all allergists would not be satisfied nor happy. A disgruntled few might permit personalities to outweigh professional loyalties. At present, the situation would not be harmonious nor conducive to united strength. The success and permanency of any merger is proper timing. It is advisable that we continue to explore the desirability and practicability for amalgamation, with an eventual decision to be reached at some time in the future.

There is one problem that has faced this College for the past several years: separate certification! I would like to discuss this with you from a practical standpoint in order that you may be acquainted with the major contingent features. The obvious and repeated failures to obtain our objectives are not due to the lack of industry and personal sacrifice on the part of the members of the Joint Committee on Certification. In fact, Chairman George Piness and members of his committee have been most persistent, most aggressive, and, at the same time, profoundly humble and patient.

It has been necessary to modify our petition for an American Board of Allergy from time to time to conform with current conditions acceptable to the Advisory Board for Medical Specialties and other interested sources. These changes have removed some of the desirable paragraphs from our original petition. We have divorced our thoughts from all consideration of a "Grandfathers' Clause." We have agreed to require certification by the American Board of Internal Medicine or the American Board of Pediatrics as a prerequisite for an allergist to be examined in allergy by allergists. Under these circumstances, it would seem that such certification would be, in reality, sub-certification. However, several recognized, separate boards have been initiated by these measures, with prior certification in other boards eventually becoming unnecessary.

In February, 1956, representatives of the Joint Committee again appeared before the Advisory Board for Medical Specialties. It is important to emphasize that for the first time encouragement was given to our application, though the eventual decision was not immediately favorable to our cause. However, the door to separate certification has been opened by the Advisory Board in their recommendation that a coordinating and regulating agency be formed. The substance and machinations of this agency will be reported to you by the chairman of the College component of the Joint Committee on Certification.

To provide assurance of continued equality with other specialty groups, it is highly desirable that allergy certification be accomplished within the framework of the Advisory Board for Medical Specialties. Our certificates

must place us on equal footing with the other specialists in organized medicine. The College component of the Joint Committee has been mandated to provide means for certification in the specialty of allergy. If this cannot be acquired by petition and application, then it must be realized by independent initiation and creation.

What is to be expected with the eventual establishment of a certifying board? The standards must be as high or higher than those required by certifying groups of other recognized specialties. The founders' group should consist of those physicians now sub-certified by existing boards. In keeping with high moral and ethical standards, certification for any candidate should be by examination and only by examination. The allergist who really wants a worthwhile board would not accept certification if it were given to him because of his age or his reputation. Membership or fellowship in either the College or the Academy is not, of itself, evidence of eligibility of any candidate for examination.

In my opinion the progress to be reported by the Joint Committee on Certification is significantly encouraging. My own recommendations have been endorsed by the Board of Regents. They are: (1) that the College accept and endorse the suggestions of the Advisory Board for Medical Specialties; (2) that an Advisory Council on Allergy be formed if this measure can be recognized as the assured preliminary step to the formation of our own separate board of allergy within the framework of the Advisory Board for Medical Specialties. Regardless of my beliefs, I assure you of my complete support of any program established by the American College of Allergists.

It has been my pleasure to have been of service to you, and I thank you for having given me this privilege and honor. There are many individuals to whom a special expression of my gratitude is extended. My wife and children have been most patient and understanding on those frequent occasions when College affairs have had priority over family responsibilities. Each past-president has been most generous in giving me the benefit of his advice and experience. Doctor Homer Prince, the chairman of the Board of Directors, has been a most reliable guide, and I have been dependent upon his sound judgment and counsel in directing College policy and decisions.

A special word of deep appreciation is due to the president-elect, Doctor Ethan Allan Brown. His remarkable capabilities, his boundless energy, and his singular devotion to the American College of Allergists have been dependable supports at all times. With his leadership we are assured of efficient management of College affairs in the coming year.

The members of the Board of Regents have been most helpful in their decisions. My thanks to each of them is only a token of my esteem and my gratitude.

I am deeply indebted to Doctor Fred Wittich, to Mr. Eloi Bauers and to the executive office staff for their cooperation and their thoughtfulness

in my behalf. Doctor Morris Kaplan is to be congratulated upon the quality of the 1956 Instructional Course which preceded this annual meeting. My sincere thoughts of appreciation are extended to Doctor Peshkin and to Doctor Rapaport for the manner in which they have completed the local arrangements for this Congress. I am aware of the fine work that has been done by Mrs. Morris Kaplan and her committees in arranging a successful meeting of the Women's Auxiliary. Doctor Lester Bartlett is deserving of our gratitude in the completion of his task as Secretary of the Allergy Session of the American Medical Association. I am grateful to each committee chairman whose endeavors have added to the advances the College has made. The accomplishments of this year reflect your thoughtfulness, your cooperation and your loyalty to The American College of Allergists.

1320 Second Ave. S.E.

THIRD CONGRESS, INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

The Third Congress of the International Association of Allergology, under the presidency of Dr. Samuel M. Feinberg, Chicago, will take place at the Medical School in Paris, October 26 to November 1, 1958. The program will be composed of symposia and section meetings on clinical and immunologic phases of allergy. Facilities for scientific and commercial exhibits will be available. The Congress Organizing Committee is headed by Dr. Bernard N. Halpern, Chairman, and Dr. André Holzer, Secretary. Professor Pasteur Vallery-Radot is Honorary President.

For local (Congress) details address: Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris VII°, France. For general information, program details, et cetera, write: Dr. José Quintero Fossas, Secretary General, Paseo 313, Vedado, Havana, Cuba, or Dr. Samuel M. Feinberg, President, 303 E. Chicago Avenue, Chicago 11, Illinois.

LABORATORY MANUALS FOR SALE

Dr. Stephen D. Lockey still has available a few copies of the Manual of Office and Laboratory Procedures, which was used in his laboratory course during the Twelfth Annual Graduate Instructional Course in Allergy at the Hotel New Yorker, New York City, April 15-17, 1956. These manuals can be purchased for $4.00 each, plus twenty-five cents postage. All profits from the sale of these manuals go directly into the treasury of the College. Books may be purchased directly from Dr. Stephen D. Lockey, 60 North West End Avenue, Lancaster, Pennsylvania.

Editorials

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

RESEARCH IN ALLERGY

Although the allergist will always be an expert in the harmfulness of harmless substances, his field is gradually extending ever more widely into other specialties. At one time, his chief interests were botany and immunology. Within a decade he has made himself an authority on the subject of treatment with antihistaminic and antibiotic agents, and the steroid hormones. His basic interest in immunology has helped him to unravel the problems of drug allergy.

Two recent pieces of research may point the way to what lies just over the horizon.

Fink, of the University of Colorado, has implanted malignant cells into the tails of mice. Following caudectomy, before metastasis, second transplants do not "take." Frozen and dried malignant cells can be extracted and, added to Freund's adjuvant, used to sensitize mice, who, when challenged with live cells, react anaphylactically. The uterine horns react violently following Schultz-Dale *in vitro* techniques.

Makari reports separately on the use of the Schultz-Dale test for the detection of specific antigens in sera of patients with carcinoma.

At Johns Hopkins, the sera from 654 patients, some normal, some suffering from carcinoma, and some from other disorders, were used as antigens. Guinea pig horns had been sensitized either actively, or by injections of extracts of ovarian, bronchial, or intestinal carcinomatous tissues, or passively by sera of rabbits or guinea pigs similarly injected.

The reaction was positive in 96 to 97 per cent of the known cases of carcinoma, and in 4 to 5 per cent of cases of suspected carcinoma, and in 4 to 5 per cent of cases of other disorders. Within a year, four out of nine suspected cases proved to be carcinomatous.

The allergist of the future may not test and treat cancer, but it is interesting to speculate on the number of specialties in which his diagnostic and treatment methods have been applied. Only the future can tell us of which of these he will become a part.

BLISTERS: POISON IVY OR PHENYL MERCURIC ACETATE?

New chemical compounds and new uses for older ones are introduced in an endless array into our daily life. Keeping informed about their possible toxic or sensitizing properties has become a troublesome, but necessary task for the allergist. The difficulty is neatly exemplified by a

recent experience of a physician friend of this writer concerning a problem of etiologic diagnosis which well may arise in any allergist's office. For this reason, it is recounted here:

My friend did a Sunday's work in his garden. On Monday, he arrived in the hospital with a beautiful crop of blisters on his hands. The diagnosis was poison ivy dermatitis—until another physician, who happened to have personal experience with the agents used for the killing of crab grass, inquired whether a beautifying operation had been done on the first physician's lawn. When this was conceded, and the spray used had been ascertained, the proper diagnosis was established: Blisters caused by contact with phenyl mercuric acetate.

Phenyl mercuric acetate has found many applications in industry and agriculture as a fungicide. It is, for instance, widely used against fungal plant diseases, such as rusts, and as a preservative in paints and in the manufacture of pulp and paper. More recently, it has also been found to be of value as a weed killer and is sold under various brand names as a spray (in 10 per cent solution) against crab grass.

It is known to cause blistering if concentrated solutions come into contact with human skin. Commercial preparations carry labels with appropriate warning. Protective clothing (gloves, etc.) is recommended for those whose occupation entails handling of this chemical. Washing with warm water and soap is suggested after accidental contact with the agent.

Though there seems to be variation in individual susceptibility, this writer has no information about true allergic (contact) sensitization.

NEW INDIAN DRUG DESCRIBED

Published in the *Indian Journal of Medical Research* (44:283 April, 1956), is a brief paper with seven references. It may or may not rank with the first paper on the properties of the Chinese plant Ephedra or the Indian plant Rauwolfia. Drs. Sirsi and Rama Rao describe the anti-anaphylactic properties of an Indian medicinal plant named *Anisochilus cornosus,* otherwise known as Ajapada.

The fresh juice of the leaves of this aromatic herb is used to relieve itching and urticaria. Infusions of the leaves and stems are useful in coughs and colds. A pharmacologic study proves the essential oil of the plant to possess musculotrophic, neurotrophic, antispasmodic, and antihistaminic activities with slight local anesthetic action.

Using egg-white as an antigen, and guinea pigs as test animals, the authors demonstrate complete inhibition of anaphylactic reaction of the guinea pig ileum, but no effect on the anaphylactic reaction of guinea pig uterus.

They discuss the concept of internal and external histamine action and

the failure of antihistaminic agents to affect anaphylactic responses in smooth muscle as in the bronchials, the uterus, and the gut, in which the released histamine affects the cells as contrasted to the favorable response in the skin and nasal mucous membranes in which the initial reaction is usually due to histamine released elsewhere in the body.

Anisochilus cornosus evidently possesses properties antiallergic in nature, more potent as an antihistaminic agent than an antianaphylactic, although it differs from these in affecting smooth muscle of the gut. Only further study will prove the action as truly antihistaminic or anticholinergic, or anesthetic or directly musculorelaxing. It was concluded that the oil may be useful in the relief of the intestinal manifestations of allergy. Only time will tell.

Meanwhile, the search for natural, as well as synthetic, drugs continues with the aim of giving symptomatic relief to the allergic patient.

About five per cent of ourselves consists of a tube with attached chemical factories, for taking in raw materials in the shape of food, and converting it into the form in which it can be absorbed into our real interior. About two per cent consists in arrangements—windpipe and lungs—for getting oxygen into our systems in order to burn the food materials and liberate energy. About ten per cent consists of an arrangement for distributing materials all over the body—the blood and the lymph, the tubes which hold them and the pump which drives them. Much less than five per cent is devoted to dealing with waste materials produced when living substance breaks down in the process of producing energy to keep our machinery going—the kidneys and the bladder and, in part, the lungs and skin. Over forty per cent is machinery for moving us about—our muscles; and nearly twenty per cent is needed to support us and to give the mechanical leverage for our movements —our skeleton and sinews. A relatively tiny fraction is set apart for giving us information about the outer world—our sense organs. And there is about three per cent to deal with the difficult business of adjusting our behavior to what is happening around us. This is the task of the ductless glands, the nerves, the spinal cord and the brain; our conscious feeling and thinking is done by a small part of the brain. Less than one per cent of our bodies is set aside for reproducing the race. The remainder of our body is concerned with special functions like protection, carried out by the skin (which is about seven per cent of our bulk) and some of the white blood corpuscles; or temperature regulations, carried out by the sweat glands. And nearly ten per cent of a normal man consists of reserve food stores in the shape of fat.—JULIAN HUXLEY: *Variations on a Theme by Darwin* 1933.

Progress in Allergy

FOOD ALLERGY

A Review of the Literature

ORVAL R. WITHERS, M.D., F.A.C.A.
RALPH HALE, M.D., F.A.C.A.

Kansas City, Missouri

WE ARE aware that a number of excellent articles on food allergy, or some phase of this subject, have been omitted. However, in compiling this review, it was found impossible to include all the references. With the exception of the historical considerations and references cited in various articles, we have, for the most part, included only the material published during the past ten years.

HISTORICAL CONSIDERATIONS

Long ago clinicians observed and recorded symptoms due to food, which are now recognized as allergic in nature. Such conditions as asthma were reported by Floyer[63] in 1717, Miller[117] in 1769 and Salter[180] in 1864. Gastrointestinal disturbances possibly due to food allergy were also reported by Floyer and Salter in their reports on asthma as cited above and also by Hutchinson[88] in 1884. Urticaria and angioneurotic edema and purpura resulting from ingestants were probably first reported by Willan[228] in 1808. Henock,[80] in 1868 and again in 1874, emphasized the association of gastrointestinal symptoms with purpura and attempted to demonstrate a clinical entity. Several of these cases were apparently the result of food sensitivity. Osler,[132] in 1888, stated that the skin manifestations, such as erythema, urticaria, angioneurotic edema, purpura with abdominal crisis and arthritis pains, were all the result of a single pathologic process, which may result from food in some instances. These early reports for the most part are descriptive accounts of clinical findings. An understanding of the mechanisms involved was made possible by the familiar experiments of Richet, who coined the word "anaphylaxis" in 1902. The discovery of anaphylaxis by Richet and Portier was not followed immediately by the realization that food idiosyncrasy could be explained on that basis. It was in 1910 that Doerr suggested a common basis for food idiosyncrasy and anaphylaxis. Vaughan found it especially interesting to learn that both Doerr and Richet, two early students of anaphylaxis, were sensitive to egg.[222] Schloss[182] was one of the earliest American clinicians to recognize the importance of food allergy and was the first to employ skin tests to foods in a systematized manner as a diagnostic measure in medical practice. He was also quick to recognize the limitations of skin sensitivity as a guide to hypersensitivity of the tissues in which symptoms arose and throughout his life continued to warn against abuse of the skin test.[74] In 1919, Richet's son, together with LaRoche and Saint-Girons, published the monograph, "Alimentary Anaphylaxis." This book summarized and correlated the contemporary European experimental and clinical information which had accumulated during the seventeen years following the elder Richet's

discoveries, and appears to be the first review of food allergy. We are indebted to Dr. and Mrs. Albert H. Rowe for their translation of this monograph into English.[98]

ETIOLOGY

Food allergy can affect anyone, regardless of whether there is an hereditary predisposition. Almost any food can produce an allergic reaction in practically any tissue in the body. Although there is a difference of opinion regarding which foods most frequently cause symptoms, it is generally agreed that the foods used most often in the diet are usually the most common offenders. These are the basic ones, such as wheat, egg, milk, potato, beans, tomato, and chocolate. The basic foods vary to a certain extent, depending on the age of the patient, his nationality and geographic location, as well as the frequency with which the food is eaten.

In discussing the extrinsic factors in bronchial asthma Spain[109] reported his findings in regard to foods. He noted that occasionally, occupational varieties of asthma may develop from the inhalation of dusts from foods, such as cereals, nuts, coffee, tea, spice, malt, and hops. Such asthma often proves implacable and stubborn to treatment, forcing the victim to abandon his occupation for another. This author states that also the absorption of a food excitant through the intact unbroken skin, in rare but important instances, may lead to asthma or other allergic conditions. Egg, beef, nuts, seeds, banana, citrus fruits, celery, white potato, and other fruits and vegetables, especially in food handlers, may excite asthmatic attacks by contact with the skin.

Usually, however, foods act as allergens by ingestion. While any edible substance may cause asthma, this investigator found that egg, milk, seafood, chocolate, and nuts are the most important, not only because of their high incidence as excitants but also because of the severity of symptoms which they produce. Bronchial asthma due to a food allergy may occur at any age but it is chiefly a problem of the first two decades of life. According to Spain, food sensitivity tends to disappear in later life. He contends that while a significant characteristic of asthma due to inhaled substances is the promptness with which symptoms appear on exposure to the allergen, this feature is present only in about half of the food cases. In the other half, the reaction is delayed, and twelve to forty hours may elapse between the ingestion of the food and the appearance of symptoms, a situation which renders identification of the food factor difficult. By cross questioning, by skin testing of the patient, and by clinical trial methods, the offender may be discovered. Despite these procedures, this clinician feels that the results in such cases are often disappointing.

The influence of heredity is equally as important in food allergy as in allergy due to other allergens, particularly so in such clinical manifestations as asthma, eczema, and migraine, according to Tuft.[207] This is verified, too, by reports of whole families being sensitive to such foods as egg or milk or, as in one instance, where the milk sensitization was transmitted through four generations. Although the hereditary influence merely provides the individual with a tendency to become sensitized, this author contends that actual sensitization may follow not only from repeated or excessive contact, but at times by other less known methods. For example, the overindulgence in certain foods by the mother during

pregnancy may result in sensitization of the fetus *in utero* and may account for the eczema and asthma occasionally affecting newborn infants. Sensitization in infants may also arise through the transmission of minute amounts of sensitizing allergens in the mother's breast milk, according to this author. While hereditary predisposition is important in many patients with food allergy, it may be insignificant in other individuals in whom temporary clinical manifestations of food allergy like acute urticaria may follow the ingestion or overindulgence of foods such as fish or seafoods. This type is more common in adults and is a sensitization induced or acquired often in the absence of hereditary predisposition from excessive allergenic contact, as the intermittent eating of large amounts of such uncommonly eaten foods as honey, strawberries, mushrooms, or shellfish. He concludes that the symptoms resulting from such sensitization often disappear in a short time leaving little or no trace of clinical sensitization.

In discussing the modes of acquisition of food allergy, Ratner[149] contended that it is not strange that some should have been tempted to the conclusion that the hypersensitiveness of the newborn is entirely due to constitutional factors, in the absence of evidence to show that the first contact may occur *in utero,* after germination and before birth. He has shown that the guinea pig fetus can be sensitized both actively and passively, first by injecting females with antigens during pregnancy, and second by feeding pregnant guinea pigs protein foods foreign to their diet. Hypersensitiveness thus acquired *in utero* he has designated as congenital allergy. It is acquired by the fetus during intra-uterine life and does not result from any character carried by the germ plasma. He concludes, therefore, that it must be carefully distinguished from the chromosomal inheritance.[157] This investigator demonstrated that the human fetus can be actually sensitized to protein-containing foods ingested by the normal woman during pregnancy and that the human fetus can be passively sensitized *in utero* through antibodies present in the blood of an allergic mother. It is believed that this explains some of the cases of infants who manifest allergic symptoms upon taking of food for the first time. Ratner emphasized "some" because he wishes to make it clear that he at no time proposed that all cases of allergy can be attributed to sensitization acquired *in utero,* but rather that certain individuals may be sensitized at that time if certain conditions are fulfilled.

ALLERGIC REACTIONS TO UNUSUAL FOODS

Food is a common allergen. Clinical experience has revealed that any food may be the chief cause or a complicating factor in almost any allergic disease. The commonly used foods are usually the causes of allergic symptoms. However, symptoms may also result from infrequently used or unusual foods.

Sugarman[197] reports a case of recurrent edema of the buccal mucosa and large aphthous ulcers in the right side of the mouth due to chewing gum which contained mint. There were no teeth on the right side. The lesions were repeated on several clinical trials.

Clinical sensitivity due to buckwheat is not extremely uncommon,[189,215] and it may cause symptoms by either inhalation or ingestion. Skin reactions to this food are frequently strongly positive. Ordman[129] described three cases which were all clinically sensitive to the inhalation of flour and two of which were also sensitive by the ingestion of this product. Skin tests were strongly positive in all three patients to buckwheat flour

extract. Buckwheat is not a true cereal but belongs to the family Polygonaceae. Rhubarb and also rumex, the weed, or docksorrel are also members of this family.

According to Yvitsky,[236] a rare hypersensitivity reaction due to sesame seed was reported by Rubenstein.[179] In this case, attacks were brought on by the ingestion of a confection known as Halvah and also by an Italian-French bread, both of which contained sesame seed. Severe shock and edema of the glottis were the chief symptoms, although intense erythema and itching of the skin were also prominent.

Hopkins[86] reported a case of contact dermatitis due to mushrooms. A lesion first appeared on the hands used to pick and pack mushrooms, and soon caused severe inflammatory reaction of the eyelids as well as the hands. Clinical and patch tests were positive and the patient remained symptom free when he avoided mushrooms.

Horesh[87] reported nine cases of dermatitis in which the symptoms were provoked by the inhalation of vapors or odors from either cooked or raw foods. He observed that some foods acting as inhalants at times may cause exacerbations when the patient is clinically sensitive to that food. He observed that keeping the infant out of the kitchen when foods were being prepared was usually sufficient to control the symptoms. He has reported that investigators have observed the following foods as inhalants that have produced allergic symptoms: egg is a common and sometimes severe offender; also shrimp peas, beans, lentils as well as foods in the raw state which form dust, such as wheat, flour, or rye flour and soybean meal. Whether the amount of antigen taken in by inhalation of the odors or vapors is sufficient to produce sensitivity is unknown, but it probably can do so.

The problem of allergy to alcohol is difficult to study because of the pharmacological activity of alcohol. In a series of experiments by Dees,[48] designed to circumvent this difficulty, she was able to conclude only that allergic and histamine wheals are increased after ingestion of alcohol. She states that it might be inferred from this that in so-called alcohol-sensitive persons the ingestion of alcohol merely brings to a clinical level a subclinical allergic reaction. Many of the reported reactions to specific alcoholic beverages reviewed by Dees appear to be due either to extraneous substances present in the beverage or to substances from which the beverage was derived. In keeping with this observation, Brown[27] reported a patient sensitive to grape and grape products including wine. Randolph[145] wrote that reactions of intolerance to small amounts of specific types of alcoholic drinks are indicative of specific sensitization to the food sources from which the constituent alcohols and flavors are derived. He also postulated that masked food allergy is a basic mechanism of chronic alcoholism.[144] In a survey of the literature on the immunological properties of alcohol, Robinson[166] found few reports that are familiar in the English language, but a number of them in the foreign literature. This author describes experimental work of Nagle[125] and Kelley and Barrera[93] on skin tests with alcohol to determine physiological susceptibility, and concluded that, although the consensus is that a strong reaction to the alcohol skin test signifies low tolerance and a weak reaction high tolerance, it has not been shown that there is any relationship between the degree of the reaction and the occurrence of abnormal response to alcohol.

According to Zindler and Colovos,[238] among twenty-eight cases of anthocyaninuria, twenty-six were related to beet allergy. Five of these

patients were sensitive to beet sugar. These investigators accept red urine as a valuable sign in the diagnosis of beet allergy. The absorption of the beet pigment from the intestine and subsequent appearance in the urine was thought by them to be facilitated by the allergic reaction. Randolph and Rollins[146] reported four cases of sensitivity to beet sugar. Three of these patients were also found sensitive to monosodium glutamate of beet origin. The latter is a condiment derived from beets, wheat, corn or soy bean and is widely used as a flavoring agent in the preparation of many foods. The principal manifestations of beet sensitivity in each of these four patients were: headache, urticaria, eczema, and severe cough with loss of consciousness, respectively.

Fries and Glaser[66] studied the antigenicity of raw and dehydrated banana. They found dehydrated banana not to be anaphylactogenic in the guinea pig, whereas raw banana produced anaphylaxis. Moreover, two atopic children, clinically sensitive to banana, could ingest deyhdrated banana without allergic manifestations. They suggested that dehydrated banana may have a definite place in the hypoallergenic diet.

Ratner and Untracht[158] found the incidence of egg allergy to be in the vicinity of 0.5 per cent in the general population and 5 per cent in allergic persons. They studied egg sensitivity in children with special reference to the increasing use of viral and rickettsial vaccines prepared from egg. In connection with this problem, they noted that, although serious reactions could result in patients already sensitive to egg,[134] the hazard of sensitization from repeated injection of vaccines prepared from egg seems negligible.[2,18,159]

Ratner and Crawford[152] conclude from experiments by the anaphylaxis methods on guinea pigs that gelatin is a non-anaphylactogenic agent. Because no authentic case of gelatin sensitization has been demonstrated in man, they were unable to obtain gelatin antibody-containing blood for human studies. They conclude that because it is non-anaphylactogenic for the animal, it must be non-allergenic for man. These workers believed that any allergenicity that might be attributed to gelatin is due to contamination with blood elements of the species in which it is derived and not to antigenicity of the gelatin itself.

Support of the view that gelatin can possess antigenic properties independent of the source from which it is derived was presented by Mendez and Hughes:[116]

> "A young woman of twenty-two complained of urticaria and angioneurotic edema which seemed to be associated with some meals. She observed that roast meat did not affect her . . . but that boiled and stewed meats were particularly irritating, and that soups and gravies made from stock also produced this effect. One other group of foods also caused symptoms—sweets such as ice-cream, 'jelly-babies,' table jellies and trifles containing jelly. A series of extracts was prepared of gelatin, peptone, ice-cream and also of various proprietary substances which would normally be used in gravies, such as Oxo, Marmite, and Bisto. On testing with these six substances, positive reactions were obtained to them all, the largest being to gelatin itself. Passive transfer sites sensitized with serum from this patient were negative for beef and mutton but were definitely positive when tested with gelatin extract of beef origin. The gelatin extract was prepared from chemically pure beef ossein sheet gelatin and was autoclaved at fifteen pounds pressure for twenty minutes."

The authors concluded that gelatin was antigenic in this case.

Although the reaction is not an allergic one, but will occur on anyone, a type of dermatitis, due to contact with parsnips, has been described. Belisario,[17] while in military service in New Guinea, saw several such

cases. The dermatitis appeared first as an erythema preceded, accompanied, or followed by a stinging sensation, which was soon followed by vesiculation and bulla formation. Careful histories revealed that the common factors in all the cases were that the patients had been peeling parsnips in direct sunlight. Patch tests with parsnip pulp and crushed seeds gave negative results. However, crushed parsnip seed, core, uncrushed seed, pulp, skin and leaves were applied to different areas and moistened for two hours in bright sunlight and positive reactions were obtained. The three prerequisites for the production of the dermatitis were: (1) Contact of parsnip material with the skin, (2) moisture, whether natural sweat, juice of the plant or water, in contact with the skin and parsnip at the same time, or moisture containing the active principle of parsnip in contact with the skin, and (3) the action of certain of the sun's rays at the time of contact or within a limited time after the contact of parsnip or its active principle and moisture. No two of these prerequisites alone will produce the dermatitis.

Death in a six-day-old infant allergic to milk was attributed by Kelvin and Schless[94] to an intravenous infusion of Amigen. The authors acknowledge that Amigen, which is a derivative of casein, could contain proteoses of casein which may have caused the anaphylaxis in this case. Coppinger and Goldner[72] reported another fatality to intravenous Amigen. In this instance, the patient was an adult. The amount used was not more than 4 cc and the reaction occurred almost immediately, terminating in death in a period of sixty minutes. The reaction presented all the classical signs of anaphylaxis.

Dextran although not a food in a technical sense, is a polysaccharide derived from sucrose through fermentation by the micro-organism, Leuconostoc mesenteroides. It has been advocated to be used by intravenous infusion as a plasma expander in the treatment of shock. Loveless[105] has suggested that dextrans might be implicated in contributing allergens to corn derivatives. Reactions of an allergic nature following intravenous use of dextran in man have been reported,[57,202] some of which were alarming, such as severe urticaria, dyspnea, cough and shock.

Ratner and co-workers[151] reported that in accordance with the results of guinea pig experiments, the antigens contained in orange seed protein and in orange juice appear to have independent specificities. Orange peel oil is non-anaphylactogenic, but does possess primary toxic properties. Orange juice, free of seed protein and peel oil, is hypoallergenic and non-toxic. In human experiments,[160] orange juice protein and orange seed protein did not appear to traverse the wall of the gastrointestinal tract readily, even when ingested in large amounts.

Wightman[234] points out the increasingly widespread appearance of soybean products in prepared foods and industrial preparations as well as the milk substitutes. He describes the findings in an adult who experienced asthma whether the soybean meal was ingested or inhaled. This patient also developed asthma on eating peas, string beans, or lima beans.

Thirty cases of vesicular eruption of the hands due to food allergy were reported by Flood and Perry.[62] The clinical picture was the usual one of recalcitrant eruption of the hand, with deep vesicules, patches of eczematous dermatitis, and varying degrees of secondary pyogenic infection. Pruritus was an outstanding feature. The authors admit that all cases of vesicular dermatitis of the hands are not due to foods. They found, however that after contact allergy, fungi and psychosomatic

factors were ruled out, food allergy was often of etiologic importance in some cases.

Bronchial asthma in a nine-year-old boy who was clinically and skin-sensitive to fennel and fennel seed was reported by Levy.[102]

INCIDENCE

The incidence of food allergy in the general population and in allergic individuals varies with different observers. Feinberg[58] stated:

"While we do not believe it to be so common as some authors indicate, we are decidedly of the opinion that food allergy occurs frequently and is a cause of one complaint or another in a large percentage of the general population. Major and chronic complaints from food allergy are also common. It is our belief that at the present time in a large group of conditions, such as gastrointestinal complaints, headache, urticaria and general malaise, insufficient importance is given to allergic causative factors. This has undoubtedly been the result of the failure of the skin tests to give reactions of diagnostic value in many of these conditions. The age of the individual has an important bearing on the incidence and possibility of food allergy. In the infant, foods are the most common allergens. As the infants become older, inhalants begin to play a part in the causation of allergic manifestations. When adult life is reached, the inhalants have superseded the foods in importance as allergens. This does not mean, however, that this applies to all allergic complaints. In certain conditions such as urticaria, gastrointestinal complaints and headaches, foods constitute the most important allergic causes, even in adults."

In 1949, Tuft[206] wrote that it was extremely difficult to estimate the exact incidence of food allergy among the general population for several reasons. He continued, and your reviewers quote him verbatim:

"In the first place, there is no uniform agreement in the literature as to its existence or frequency—certain observers (e.g., Cooke) believe it to be uncommon in adults, whereas others (e.g., Rowe) think that adults are commonly affected Likewise, some doubt that food allergy is of etiologic importance in such conditions as migraine, colitis, purpura, arthritis, etc., whereas all agree that there is a definite relationship in patients with asthma, eczema, or urticaria. This disagreement exists largely because the evidence for such a relationship has been based more upon the results of skin tests than upon clinical trial. Since skin tests with food allergens may be negative despite the existence of definite clinical proof of allergy to food, the existence of any evidence based upon such results would be misleading. The incidence, therefore, probably is much higher than is generally given, since it depends upon such factors as age of the patient, the condition being studied and the results of skin tests (or the lack of them). The incidence of food allergy depends greatly upon age; thus, it is a more common offender in children than in adults and much more frequently so than the inhalant allergens."

Squier[192] writes that the role of food allergy in adults has been a controversial subject with allergists for years. In fact, some physicians believe that food allergy is clinically important only in young children and insist that foods rarely are responsible for allergic symptoms in adults. At the other extreme are those who insist that food allergy is a major and frequently unrecognized cause of clinical symptoms in adults as well as in children. He contends that some physicians not only attribute to food allergy such recognized allergic symptoms as asthma and rhinitis, but in addition regard many vague subjective complaints as probable results of allergic reactions to foods. This author agrees that most physicians recognize that food allergy is important in some patients and also that there is uniform agreement that during childhood allergic reactions to foods are of major importance and often are the sole cause

of allergic symptoms. He shares the opinion of other workers, in stating that after childhood, however, it is believed that a progressive reduction occurs in the frequency and importance of foods as a cause of allergic reactions. Indeed, there are some who regard food allergy as essentially non-existent in adults, and accordingly do not give serious consideration to food allergens as a possible cause of symptoms. Squier comments that this extreme attitude is not justified and may result in diagnostic errors due to prejudice just as the uncritical bias of others may lead to unnecessary and sometimes harmful food eliminations. He contends that the reported frequency of food allergy in adults is affected not only by the diagnostic criteria used, but even more by the experience and attitude of the physician. The description of symptoms of intolerance given by a patient may be attributed by one physician to food allergy, while another might consider the same statements to be evidence of a gastrointestinal neurosis.

Chobot[37] finds that the incidence of food allergy is a much disputed question. He contends that some observers, as Rowe[117] and Vaughan[220] place the incidence very high, about 40 to 60 per cent of allergic patients, while the majority of qualified students regard this as much too high and place it more nearly in the range of 5 to 10 per cent of the allergic patients. This author lists the reasons for this discrepancy as follows: a too liberal interpretation of what constitutes a positive skin test; a misinterpretation of coincidences which are curiously common in medical practice, and the difficulty of established and proven diagnoses.[11] He also contends that in infants, sensitization to foods is relatively high and ranks in importance with infection, while after five years the food sensitization tends to spontaneous disappearance, making the incidence of clinical food allergy low in relation to that caused by inhalant substances and infection.

According to Rinkel,[162] the incidence of food allergy in patients with common allergic syndromes may vary from only one sensitization in the more fortunate allergic person, to practically every food used regularly by the patient. Contrary to general opinion, he contended that the number of foods to which one becomes sensitive increases with age—adults having more food allergies than children. In hay fever, the average is about five foods; in perennial nasal allergy it is nearer seven, while in asthma it is above ten per patient. The author suggests that this is what would be expected, since the frequency of use of a given food is a major factor in precipitating an allergy to it. There are several other conditions which influence the development of food allergies. These are infections, particularly measles, whooping cough and especially influenza. These, however, are dependent upon another factor which the author has called "the inherent tolerance for foods."

A poll of the allergists by Loveless[105] revealed that clinical symptoms from ingested corn were encountered in only 0.16 per cent of their 45,000 patients. This stands in marked contrast to an incidence of 16 to 30 per cent, i.e., 100 times more frequent, as reported by Rinkel, Randolph, Rowe, and Crandall. Some explanations for this disparity have been uncovered by her experiments with objective feeding tests. It was found that extraneous factors, especially of psychological origin, can complicate the diagnosis unless the patient is subjected to repeated studies, to masked ingestions, and to placebo meals. Whereas, no evidence was found for the allergenicity of corn oil, syrup, or sugar, clinical reactions, to her surprise, were encountered following the controlled ingestion of the several starches employed for her studies. Love-

less contends that the clinical significance of this type of hypersensitivity would not appear to have the practical importance assigned to it by Randolph and his school. For one thing, its occurrence was rare even among the group of patients who were selected on the basis of their marked allergy for whole corn and who were tested with relatively huge ingestant doses of starch. Randolph has claimed that provocative amounts of starch allergen escape from paper cartons into milk, sauerkraut, and frozen foods. This author comments that it seems unlikely that their cornstarch-reactive cases would have been affected by such traces. At any rate, it is her feeling that the incidence of clinical susceptibility ought to be far lower with such small amounts of this substance than with the 10 gm of cornstarch involved in their test puddings.

Differences of opinion regarding the recognition of food allergy seem to result from the perpetuation of several misconceptions according to Randolph.[141] First, there is the impression that food sensitivity is concerned primarily with children, whereas, actually, it is at least as common and usually more complicated in adults, in view of the multiplicity of foods involved and the greater interrelationship with malignant allergy. Second, there is the prevalent notion that patients will be able to detect the existence of sensitivity to an article of the diet. This is commonly true with foods eaten occasionally, but a patient rarely suspects sensitivity to a food ingested at frequent intervals. The third misconception in reference to food allergy deals with the literal interpretation of skin tests with food extracts. When skin-test results are checked in patients carefully diagnosed on a clinical basis, both false positive and false negative reactions are seen to occur with such frequency as to cast serious doubt on the ability of cutaneous or intracutaneous tests to indicate specific current sensitivity.

Several misconceptions have distorted the current recognition of food allergy. Contrary to prevalent impressions, food sensitivity is a common cause of symptoms at any age, the history cannot be relied upon to detect sensitivity to specific foods or to rule out that possibility, skin tests with food extracts are not reliable diagnostic procedures and do not constitute an essential part of an allergic investigation, and, lastly, food allergy not only exists in a selected group of foods such as wheat, milk and eggs but may involve any article of the diet and usually does so with an expected incidence in direct proportion to the frequency of ingestion of various foods; this is according to Randolph.

According to Moore,[121] who analyzed 1,000 consecutive case records of infants seen in private practice, 383 had proved allergic reactions to foods. His comment is that this figure is undoubtedly higher than a similar analysis in many offices would reveal because many infants known to be allergic who are not under routine care in their office probably distorted the figure. However, it does indicate that allergic reactions to food during the first year of life are not at all uncommon.

Loveless,[106] having polled 191 allergists and pediatricians, concluded the incidence of allergy to milk is low, amounting to only 1.5 per cent when diagnosed by clinical standards and at 2.3 per cent by cutaneous methods. By inference, the occurrence of this malady must be rare among the general population. Such a statement stands in striking contrast to the opinions of Randolph, Rinkel, and Rowe who regard milk and food allergens as highly important excitants. One reason for this is that they include signs and symptoms which generally are not accepted as allergic by most physicians. Among these are fatigue, drowsiness, headache, chilly

sensations, and pains or "drawing" of the muscles. This investigator certainly gained the impression that allergy for milk is unusual when she was trying to locate subjects suitable for ingestion studies during the past one and one-half years; only twenty patients were procured. Loveless warns that no effort to determine the true incidence of milk hypersensitiveness will be rewarding until more scientific means of diagnosis than those in current use have been found.

In a very interesting discussion on the incidence of allergy to cow's milk, Collins-Williams[36] draws attention to the fact that it is extremely confusing because of the wide variation in the reported incidence. He contends that this variation is due partly to the criteria used for diagnosis, since the diagnosis is largely a clinical one and is therefore likely to be influenced by the enthusiasm or lack of it on the part of the observer for allergy. More important, the estimate of incidence is also influenced by the pediatric population under observation. In the practice of medicine it is almost impossible to have a completely unselected series since, if one has a reputation as an allergist, it is inevitable that one will have more allergy in his practice than the other pediatricians in the same center. The same applies to those having a reputation for the care of newborn infants, for the treatment of diarrhea, for the treatment of colic, et cetera. Therefore, this observer rightly contends that it is impossible for any one observer, regardless of how honest his appraisal is, to give the true incidence of allergy to cow's milk. The following are some very interesting comments of different observers as reported by Collins-Williams:

"Bain[16] states that milk is the most common single offender in eczema in infancy and childhood, and Hill[84] that it is the most important factor in many cases of infantile eczema. Davidson[45] found that milk produced symptoms in 40 per cent of 100 children over six years of age with perennial allergic symptoms and in 55 per cent of twenty allergic children up to four years of age, and concludes that in allergic syndromes of perennial occurrence there is a 40 per cent or better chance of milk allergy playing a leading rôle in producing the symptoms. Buffum[149] states that milk is probably the commonest food cause of wheezing in babies and that colic and vomiting in early infancy strongly suggest milk allergy. Rosenblum and Rosenblum[169] concluded that cow's milk was the most common offender in sixty infants with gastrointestinal symptoms and eosinophils in the stools. Rothman[170] feels that milk allergy is a common cause of allergic diarrhea. Wessel and associates[227] found allergy to be the chief cause of colic in 12 per cent of forty-eight infants who suffered from colic and a contributing cause in another 19 per cent, and this allergy was presumably usually to milk since these were small infants. Hill,[156] on the other hand, feels that gastrointestinal symptoms such as vomiting and diarrhea are only occasionally caused by allergy. Clein[32] states that approximately 7 per cent of infants are allergic to cow's milk in some degree. Donnally[51] and MaGee[149] that cow's milk is a comparatively frequent offender, Martin[113] that allergy is an important cause of infantile colic. Chobot[30] believes that milk sensitivity is a common occurrence. Rowe[174] finds that cow's milk allergy occurs in 20 to 30 per cent of all food-sensitive individuals and that infantile colic is often due to milk allergy. Loveless,[106] by means of a questionnaire sent to physicians, largely specialists whose encounter with allergy would be maximal, found an incidence of milk allergy of 1.5 per cent among 245,000 patients, both adults and children, by clinical standards, and of 2.3 per cent among 180,000 patients by skin tests. Vaughan and Black[223] reported a questionnaire sent out by the Bureau of Health and Public Instruction of the American Medical Association in which the following estimates of the incidence of milk sensitivity were made: In children, Cooke estimated an incidence of 0.3 to 0.4 per cent, Rackemann less than 0.1 per cent, Waldbott 3 to 5 per cent, and Rowe 2 to 7 per cent. Vaughan, in the normal population of children and adults, estimated 1 to 1.5 per cent and Alexander, in a large gastrointestinal clinic serving adults and older children, estimated 5 per cent."

UNCOMMON MANIFESTATIONS DUE TO FOOD

It is generally recognized that food may be the chief cause or a complicating factor in the common so-called "atopic" conditions, such as chronic or seasonal nasal allergy, asthma, and certain forms of headaches, gastrointestinal disturbances, eczema and urticaria. There are a number of less well-known conditions however, which, according to the literature, also appear to be due to food allergy.

Otologic symptoms may be either of allergic origin or complicated by allergic manifestations. Elkins[56] stated that whether the otologist worked with the allergist, or applied adequate methods himself, is less important than that ear pathology not be permitted to continue unimproved, or to continue to recur, by failure to consider allergy as having any relation to it. Derlacki,[49] regarded the allergic approach to the management of many previously considered surgical problems in rhinology as an accepted fact and now believes that a similar plan is evolving in the diagnosis and treatment of several acute and chronic disorders of the external, middle, and internal ear. In his experiences, he felt that the therapy-resistant chronic cases of external otitis, of suppurative otitis media of the benign type, and of secretory otitis media were frequently allergic in origin and often responded to specific allergic management. In contrast, however, he found that only a small number of cases of labyrinthine hydrops could be proven allergic to a specific inhalant or food. This investigator contended that the excellent results in proven allergic cases of hydrops treated with specific allergic therapy justified the consideration of allergy as a possible etiologic factor in all cases.

Theodore[203] stated that hyperemia and edema of the conjuctiva may occur in food allergies, but the ocular reaction usually plays only a minor rôle in a dramatic systemic reaction. Dean and his co-workers[46] reported six cases in which foods were demonstrated to be the causative agent of interstitial keratitis. In 1954, Wiseman and Moore[231] reviewed the literature for the cause of glaucoma. They found that food allergy was a cause in one case and a possible factor in four other cases. Retrobulbar neuritis accompanied by other allergic manifestations was found in a pork-sensitive individual by Stevenson and Alvord.[195] Juvenile cataract associated with atopic dermatitis is discussed by Bentolila and associates.[19] They presented a patient who was extremely sensitive to many foods and inhalants and commented that although the incidence of dermatitis is frequent, the mechanism which causes cataract in these cases is not definite.

Andresen,[13] in 1951, contended that it was a daily experience of clinicians and patients alike to discover that the ingestion of certain foods invariably cause such symptoms as heartburn, nausea, distention, cramps, diarrhea, migraine, as well as such directly observable lesions as canker sores in the oral cavity and ulcerative colitis in the rectum and sigmoid. This investigator emphasized that there was one outstanding feature of ordinary allergic reactions and that was their rapid disappearance upon the withdrawal of the offending factor. This may be observed in urticaria of the skin, as well as in the uncomplicated ulcerative colitis lesions as seen through the proctoscope.

Andresen pointed out that in the gastrointestinal tract, the allergic reaction may be a localized area or occur throughout the tract. Acute gastroenteritis may occur, and the reaction will continue as long as the offending allergen is being taken or remains in the tract. Usually, they are more or less localized in the mouth, esophagus, stomach, gall bladder or appendix. Milk irritations in the small intestines may produce pains and diarrhea, but

the more chronic changes may result in the typical findings of regional enteritis. The colon is frequently affected. Milk-allergic reactions, he pointed out, may be accompanied by peristaltic unrest, milk tenesmus, or diarrhea, often alternating with periods of constipation, and mucus may be seen with formed or loose stools. This syndrome is known as mucous colitis, irritable or unstable colon. Chronic allergic irritation, he related, may result in changes in the bowel wall starting with redness and edema and continuing through the stages of area ischemia, sloughing, hemorrhage, perforations, adhesions and obstructions, producing the condition known as idiopathic ulcerative colitis or colitis gravis. Andresen emphasized that a history of known reactions following the ingestion of certain foods may be of value. For example, the patient who reports heartburn after eating oranges or chocolate, or one who has nausea or vomiting after eggs or migraine after whisky, or the patient who says the milk always causes diarrhea, should all be suspected of allergy.

Lupton[111] described a case of cheilitis due to coffee. The history indicated that in addition to the persistent lesions about the lips, the patient complained of epigastric and substernal discomfort and eructation of gas. These symptoms all disappeared on the omission of coffee from the diet and returned again when it was included. It is of interest to note that a patch test to coffee in the same concentration as the beverage resulted in a positive test. The patch was applied to the flexor surface of the left forearm for forty-eight hours.

A forty-six-year-old Negro woman was in perfect health until 1934, when several small blisters appeared on the end of her tongue. In the next few years, she consulted many physicians and was given many different medications. After careful observation, it was learned that she was extremely allergic to Irish potatoes; when she ate a small amount, her tongue became "stiff and cramped at the root" and her mouth became "covered with blisters" which started as small white areas, "opened like a flower" and then became fiery red. On these occasions, her stomach burned. She also noticed that her mouth, tongue and oral mucous membrane became sore when she ate grapes, eggs, or milk. By omitting these foods, the patient stated that her life was "made worthwhile" again.[8]

According to Antia and Cooper,[15] a case of chronic rectal bleeding due to milk was described as occurring in a woman aged thirty-eight with an unusual history of bleeding per rectum every day for the past seven years. Any possibility of malingering was dispelled by punctate bleeding all over the colon, which led to the belief that it was probably an allergic manifestation. When milk allergy was suspected, all diet was stopped except that of fruit juice and water, and for the first time in seven years the bleeding stopped. Further tests showed that bleeding recurred whenever milk was given. There was an apparent lag of twenty-four to forty-eight hours between bleeding and starting or stopping of milk which these authors explained by the products of milk digestion coming in contact with the mucosa of the colon. These authors claimed that the patient had apparently been desensitized to milk by gradually increasing the amount by one drop a day.

Rowe,[178] in 1953, reported three patients with supposed infectious regional enteritis due to food allergy. The first, a woman aged forty-one, who complained of abdominal pain, cramping and diarrhea, was rapidly relieved of her discomfort and continued free of it for five years on a milk-free diet. The skin tests and the leukopenic index were negative to milk. The diagnosis was established by the history and the x-ray findings.

and later confirmed by microscopic examination of a surgically removed portion of the inflamed ileum. The next patient, a woman aged thirty, experienced symptoms of regional enteritis from the ingestion of milk, eggs and fruit. The symptoms could be reproduced at will by clinical testing. A change in physicians permitted a change in the diet. Shortly after the use of a soft general diet, the abdominal symptoms gradually increased until finally there was obstruction of the terminal ileum which resulted in resection of this portion of the bowel. For two postoperative months, the patient experienced four to six loose stools daily while using a soft diet. The authors are of the opinion that the operation would have been avoided if the elimination diet had been maintained. The third patient, a woman aged forty-nine, remained practically well for sixteen months on a fruit-free diet consisting of rice, tapioca, white potato, lamb, pureed carrots, squash, sugar, salt and water. Cortisone, given orally in doses of 25 mgs three times daily for nine days, hastened the recovery. These authors emphasized that the evidence accumulated by Andresen and Rowe over a period of years, that food allergy is a major cause of chronic ulcerative colitis, necessitates a closer study of the rôle of allergy in regional enteritis. They explained that the localization, spreading tendency, remissions and recurrences, fever, occasional inherited predisposition, and the relief obtained with x-ray therapy and cortisone can all be explained from the standpoint of allergy.

Rowe[175] found that food allergy is one cause of "unexplained fever." He pointed out that fever due to drug and serum allergy is generally recognized, but reports of fever due to food allergy that have appeared from time to time in the literature since 1911 have not been generally recognized or accepted. He presented a patient who had fever due to milk and to a less extent from chocolate, peanuts and walnuts. This patient was hospitalized because of fever for four and one-half months before allergy was suspected and proved to be the causative factor. Rowe explained that fever due to allergy was most likely due to a localized or generalized reaction in the temperature-regulating center of the brain.

In an excellent and critical review of the literature, Dees and Simmons[47] noted that allergy of the urinary tract is not commonly reported and less often proved. Although they found that allergy of the urinary tract does occur, yet, according to an unofficial poll of clinicians, it was the consensus that urinary tract allergy is very rare. Dees and Simmons believe that the apparent immunity of the urinary tract may be due to the fact that it has relatively little, if any, normal contact with foreign protein or other substances in their natural state, as is the case with the skin, respiratory, and gastrointestinal tracts. They explained that it is buffered by the other systems as well as by the blood and lymph, and only those substances which pass this barrier reach the urinary tract. However, allergy which involves the cellular reactions would find the kidney no more protected than other body tissues, and therefore they find lesions of this type as frequent in the kidney or more so than elsewhere. Nevertheless, hematuria,[10,52,95,204] bladder pain and nephritis[26] have been attributed to food in what appears to be well-authenticated cases.

Purpura caused by food allergy may be of the non-thrombopenic type either with or without associated joint involvement (Schönlein's) or gastrointestinal symptoms (Henoch's). The pathology is presumed to be in the capillaries. Thrombopenic purpura due to food, described by Dutton,[54] and Squier and Madison[193] is less well known. Yet there is evidence that the platelets can be affected by allergic mechanisms.[34,109,128] Ackroyd[6]

wrote that purpura is always due to a vascular lesion. Thrombocytopenia, when present, tends to increase the hemorrhagic tendency. He believed that the platelets and capillary endothelium are antigenically related, and therefore an antibody which injures the platelets can also damage the capillary endothelium. Thrombocytopenia and capillary endothelial damage, therefore, may have a common cause. Allergic purpura, according to Ackroyd, is of two types: (1) purpura associated with an erythematous skin lesion and also with joint and visceral symptoms: Henoch-Schönlein syndrome; (2) true purpura in which the surrounding skin is normal. Ackroyd believes that although the Henoch-Schönlein syndrome has been shown to be due to hypersensitivity to foods in some cases the majority are due to unknown causes and the allergic basis is unproved. True purpura, he contends, is rarely if ever due to foods. Ackroyd summarized the available literature through 1953 and found reports of seventy-four cases of the Henoch-Schönlein syndrome due to hypersensitivity to foods. Jensen[89] reported three additional cases in 1955, with fish or penicillin as the antigen.

Thrombotic thrombocytopenic purpura characterized by clotting of the platelets in the small vessels, lowering of the platelet count, and hemolytic anemia is a variant of thrombopenic purpura. It is clinically recognizable by manifestations of thrombocytopenic purpura, hemolytic anemia, and transitory bizarre neurological signs. Since the disease is now recognized clinically with greater frequency, allergy has been considered as a possible etiologic factor. Singer[187a] stated that the evidence to date has neither proved nor disproved that thrombotic purpura belongs to the group of hypersensitivity diseases.

Favism, or hemolytic anemia due to ingestion of fava beans or inhalation of the fava flower pollen or bean dust, is accepted as an example of an allergic affliction of the red cells. The disease has been known since ancient times, but Luisada[110] brought favism to the attention of the readers of English medical literature in 1941. By 1951, there were ten reported cases[225] in the United States. All of these patients were individuals with ancestors from the Mediterranean countries. The disease occurs chiefly in the inhabitants of the Italian island of Sardinia but is widespread among persons of Mediterranean descent.[50,112] Luisada observed that in favism a certain importance can be attributed to malaria. Nearly all people suffering from favism have had malaria and have had malarial ancestors. In establishing an allergic basis for the disease, he cites positive skin reactions to extract of the bean, pollen and leaf of the plant, capability of passive transfer both by direct testing and by feeding, and the apparent hereditary influence on sensitization. In a study of forty-four cases, Pazzi noted that a positive reaction to all extracts was never obtained in patients during an attack, but was attained a few weeks after the cessation of the attack. The patients showing reactions were susceptible to attacks either by inhalation of the bean dust or by ingestion of the bean.

Arthritic symptoms attributable to food allergy have been described by Lewin,[103] Vaughan[221] and Zeller.[237] Rockwell[167] offered suggestive evidence that the lesions of rheumatoid arthritis may be due to bacteria, inhalants or food allergy. He cited the similarity of the arthritic changes occurring in serum sickness and penicillin reactions to rheumatoid arthritis. Turnbull[213] strongly considered food allergy among other etiologic factors in the production of the arthritic condition. In his series of cases, dietary management was successful in a significant number of instances,

and he advocated allergic investigation as a routine measure in the treatment of arthritis.

Reports of food sensitivity eliciting reactions in blood vessels larger than the capillaries or in the heart are not frequent. Harkavy[37] reported three cases of migrating phlebitis due to fish sensitivity. He also reported cases of tachycardia and angina pectoris due to food allergy. According to Tuft,[206] cardiac arrhythmias have been reported as the result of allergy often enough to be more than a coincidence. Simple tachycardia, disturbances in sinus rhythm, extrasystoles, and paraxysmal tachycardia have all been reported to be due to allergy to foods.

McGee[115] reported the observations of twenty-one cases of fetal hiccoughs. The onset of the hiccoughs varied from four and one-half months of pregnancy to about one month prior to delivery. There was a history of clinical sensitivity in seventeen of the mothers. In ten cases, the mothers had allergy of the gastrointestinal tract. As a group, the twenty-one infants manifested clinical allergic symptoms early and represented difficult feeders. Ten could not take milk. The most interesting finding was the ability to reproduce the fetal hiccoughs by feeding a few of the mothers a specific food. The foods which gave rise to such reactions were chocolate, milk, tomato, grapefruit, nuts and watermelon. McGee believed that fetal hiccoughs occurs much more often than is realized. It is usually found in mothers who are, or who have been, clinically sensitive. He regards fetal hiccoughs as a warning sign that the newborn infant will probably be very allergic. He advised that when fetal hiccoughs were noted, the mother should avoid foods to which she has been previously clinically sensitive and should avoid excessive amounts of any food.

Observations made of 1,500 pregnancies indicated a definite relationship between premature uterine contraction, sometimes terminating with premature delivery or miscarriage, and a sensitivity to one or more foods according to Mundall.[124]

A patient with definite neurological symptoms was reported by Staffeiri and his associates.[194] A woman, aged twenty-nine, had suffered from nonseasonal asthma for the past four years. Also for the past three years, she experienced symptoms which alternated between asthma and recurrent painful swelling of the joints, diffuse urticaria and erythema, paresis in the fingers, and fever. There were also signs of capillary fragility: petechiae and ecchymosis of the legs and thighs, constituting a purpuric syndrome. There was paralysis of the right side of the face, and disturbance of speech. Edema, urticaria and purpura became more marked. The symptoms disappeared rapidly at times, but often twenty-four hours later the attack recurred and with the same characteristic physical findings. Subsequently, she was found to be sensitive to wheat, and she became symptom-free following its removal from the diet. To confirm the diagnosis, four deliberate test feedings of wheat were performed at intervals. The first test resulted in headaches, and later edema and purpura appeared in both legs. These symptoms subsided in three days. The second test resulted in edema, purpura and asthma which disappeared when wheat was again eliminated. The third and fourth tests produced allergic responses but no neurological manifestations.

The authors of this review have observed a patient who is sensitive to multiple foods and who experienced paresthesia of the right arm followed by severe unilateral headache upon ingestion of orange, lemon, tomato, wheat, egg or milk. At one time, this patient had persistent neurological symptoms and an elevated spinal fluid pressure necessitating

withdrawal of cerebrospinal fluid. She had been diagnosed as having a brain tumor when actually she was having repeated episodes of cerebral allergy.

Rowe[117] summarized his findings of toxemia and fatigue due mostly to foods in seventy patients. The principal symptoms observed were fatigue, weakness, lack of energy, and ambition, drowsiness, loginess, bodily aching, depression, irritability, restless sleep, insomnia, fever, chilling and night sweats in varying combinations and degrees. Also Randolph[139] discussed more extensively the allergic responses of skeletal muscle with special reference to muscles of the neck and associated headache. These symptoms were noted as a result of clinical observations on patients undergoing individual food tests for the diagnosis of specific food sensitivity. In 1954, Speer[191] presented case reports of six children showing evidence of hyperkinetic and hypokinetic response due to food allergy. Rowe[173] contends that nervous tissue allergy is to be expected when it is remembered that the blood-borne allergens to ingestants, inhalants and infectants produce primarily a vascular reaction and that no tissue of the body is exempt. He found in the literature that foods and less often inhalant and bacterial allergy were recognized causes of cerebral reactions. He cited three cases, one of whom showed suggestive evidence of cerebral reaction to celery and another to multiple foods including wheat, milk, egg and fish and the third patient was found to be sensitive to tomato, white potato, egg, citrus fruit, and melon.

Stevenson and Alvord[195] reviewed the literature of allergy in the nervous system in 1947 and reported several instances of central nervous system allergic reactions such as headache and convulsions due to foods. One unusual case was a physician who was sensitive to pork and who suffered from recurring eczema and retrobulbar neuritis with a cerebellar seizure and a slight hemiplegia with homolateral severe thalamic sensations after "inadvertently crossing the pork-line," as the patient himself stated.

Heyman,[81] in 1952, summarized the findings in twenty cases of migraine. He found that of this number, fifteen patients were sensitive to food. Pork and chocolate were the chief offenders. Glaser,[67] reporting on migraine in children, stated: "Most of the children with migraine I have seen were brought in for consultation because of allergic difficulties, the migraine being elicited only in the course of the history taking." In all instances in which the migraine could be proved to be due to food allergy, the offending foods were known by experience or were discovered, not by skin test, but by means of elimination diets. Chocolate, wheat, milk and eggs were the most frequent offenders. Schwartz[185] found the incidence of migraine among relatives of 241 asthmatic patients and of 200 normal non-allergic persons to be identical. He concluded that migraine has no hereditary relationship with asthma, and believes therefore that migraine is only rarely of allergic nature. Unger and Unger,[214] on the other hand, reported that in a group of fifty-five patients with classical migraine who have been followed for a minimum of three months, 80 per cent have been either completely or almost completely relieved of attacks by detection and elimination of the causative foods. They concluded that migraine is basically an allergic disease, although psychic stimuli may provoke individual attacks in allergic persons.

The rôle of food allergy in multiple sclerosis has been questioned. Reese,[161] in 1949, wrote:

"In our researches in Wisconsin, we have not been able to demonstrate or to obtain from patients many histories of specific allergies. Careful testing for practically

everything known in the allergy department did not crystallize into any specific allergic diathesis in multiple sclerosis. It is true that some patients dislike certain foods, some do not like dairy products or butter fats, others dislike raw fruits; however, such findings are not important for the formulation of a disease-producing allergy. Can allergy, even if it is not detectable and not proved, be excluded as an etiology? No. We can have tissues sensitized by a factor that we do not even suspect. Additional irritation by such a factor 'X' will produce an anaphylactic-like reaction in tissues with continuous hypersusceptibility to subsequent contact. This sequence produces the typical phenomena: edema, transudation of blood from irritated vessels with irritation of the nervous tissues, which would be glial proliferation and scar formation in the white nervous substance."

Ehrentheil and colleagues,[55] were of the opinion that allergen-free diet regimen based on the outcome of ophthalmic testing is a potentially helpful therapeutic procedure in their management of multiple sclerosis patients.

The possible frequency of neurologic manifestations of allergy is obtained by inference from the work of Davison[44] who analyzed case reports of approximately 5,000 potentially allergic patients and found 428 patients with possible cerebral allergy, selecting eighty-seven patients for careful study. A family history of allergy was present in seventy-two of the patients studied and absent in fifteen. This investigator proved food sensitivity clinically in fifty patients. There were other allergic manifestations than cerebral symptoms in all but four patients. The cerebral manifestations which were observed ranged from vague personality changes to definite disorders of speech and inhibition of cerebration. The ten most common foods incriminated in this series in order of their frequency were: milk, chocolate, onion, cabbage, pork, eggs, fish and shellfish, tomatoes, nuts and apples.

ALLERGENS

In an editorial on materials for skin testing, Sherman[186] suggests that allergists and other physicians should examine critically their methods and materials of skin testing in order to obtain the greatest possible correlation between clinical sensitization and skin reactions. In general, skin tests with inhalants are quite reliable, while those with food give so many reactions, both "false-positive" and "false-negative" which can not be correlated with clinical symptoms, that many physicians have come to believe that they are of little or no value. He contends that some of the reasons for these inconsistencies are explainable on the basis of a change in the antigen, during the preparation of the testing material or by cooking the food or after ingestion when certain metabolic and digestive processes take place so that no appreciable amount of the active antigen reaches the shock organ through the blood stream.

Cooke[39] has shown that definite but delayed clinical symptoms to food associated with negative skin tests has been due to a proteose or other products of digestion and not to an unaltered food. In such cases, suitable preparations of artificially digested food will give positive skin reactions. Others have demonstrated that failure to obtain positive skin tests in clear-cut cases of food allergy may be due to the failure to employ the antigens for testing in active form.

The failure to demonstrate positive skin test to certain cases of clear-cut food allergy may not only be due to changes in the antigen as a result of digestion, but also to a failure to employ the antigen in active form in skin testing. Tuft and Bloomstein[208] have demonstrated that the antigens of berries and certain other fruits were easily destroyed in the

routine preparation of extracts for skin testing. In patients with negative skin tests to standard extracts, but with known clinical sensitivities to these foods, scratch tests with a fresh juice evoked positive skin tests.

According to Strauss and Spain,[38] "the more completely the antigen in extract form retains the characteristics which it possesses in its natural state in the environment, the more precise and the more accurate the cutaneous test will be." Indeed, it would be ideal if it were possible to perform the tests with the antigens in their natural fresh state or original condition.

In keeping with the suggestions made by the above authors, Ancona and Schumacher[11,12] used raw foods as skin-testing material in allergic disorders. They have shown that when food is collected in fresh raw state and, according to its physical properties was reduced to a paste or powder suitable for scratch testing, it produced positive skin reactions of a larger size and in greater frequency than the corresponding commercial extracts. These authors found that frozen foods for skin testing could be prepared, stored and used by a simple, practical, and inexpensive method. It has been their observation that storage in a frozen state for several months and thawing immediately before using for one series of tests did not affect the allergenic properties of the material. Raw foods were found to be innocuous to the skin and non-urticariogenic in allergic as well as in non-allergic persons. It would be interesting and revealing for these investigators to make a comparative study of the clinical reactions to the foods tested with frozen raw food allergens as well as with the commercial skin-testing extracts. In a later report, Ancona and his associates[10] demonstrated positive scratch tests to crab meat in a case of purpura, although tests with the corresponding commercial extracts by scratch and intradermal tests were negative. According to the authors, this may possibly be due to the presence of a thermolabile factor in fresh food which either is removed by Seitz filtration and, therefore, absent in commercial extracts, or deteriorates in time at room temperature. It will be of interest to see this problem developed further with a greater variety of foods.

Miller and Campbell[119] found that skin tests on egg-sensitive individuals with egg white and four components (albumin, ovomucin, lysozyme and trypsin inhibitor) indicates that sensitization often occurs to only a few and, in some instances, to only one of the components. It is, therefore, important from a clinical standpoint to recognize the possibility that sensitization may occur to antigens which are not present in sufficient quantities in the crude extracts to give positive skin tests.

Bernton[20] stated that, in 1949 the Allergens Research Division of the United States Department of Agriculture reported the isolation of an active allergenic fraction from cottonseed. The technique involved in the isolation of the principal allergenic component of cottonseed has been successfully applied to several of the oilbearing seeds—almonds, Brazil nuts, coconut, filbert nuts, peanuts, soybeans, et cetera. In 1942, evidence of the presence of the multiple cottonseed reagins and of multiple cottonseed allergens was presented. The question of multiple allergens was accordingly removed from the realm of probability to the realm of actuality. This contribution is of fundamental importance in demonstrating that foods, when ingested, carry with them the allergen or allergens which react with the sensitized cells. Accordingly, he cannot subscribe to the view that clinical sensitization to protein digestion derivatives is the only basis of allergic phenomena. This author believes that the contribution by Bloom, Markow and Redner[25] were the results of skin tests of standard extracts,

when compared with their pepsin and trypsin digest, indicated possible changes in the antigenicity of foods due to digestion. He points out that their conclusion is significant: "The results of this limited study suggest that changes in the antigenicity of foods as a result of digestion, as indicated by skin tests and intentional feeding tests, are an infrequent occurrence."

Spies, as pointed out by Bernton, has called attention to certain inherent difficulties in the study of the effects of digestion upon suspected allergenic foods which must not be overlooked. They are listed as follows: the indefinite nature of protein hydrolytic products, the possible presence of immunologically significant traces of undigested native protein in enzyme digests, the use of complex foods, the lack of determination of the degree of enzyme digestion, and other difficultly controlled factors.

According to Bloom and his co-workers,[25] skin tests with inhalants yield sufficiently reliable information to be of diagnostic value, but skin tests with foods is definitely a stumbling block in their diagnostic approach to the etiology of allergic diseases. They cite instances where it has been demonstrated[41,230] that positive skin tests could be obtained with substances other than unaltered proteins when working with substances other than food. Later, however, other investigators by studies with proteoses, from known food sources, showed definite specific antigenicity in the guinea pig for primary proteoses of milk, whey, casein, beef, and chicken. It was now assumed, according to these authors, that since the products of early protein digestion (primary proteoses) were antigenic, it might be possible to explain, as due to products of food digestion, why certain clinical reactions which followed the ingestion of foods were positive and the skin tests to the original unaltered protein of such foods were negative. Using solutions of primary and secondary proteoses prepared from known sources, Cooke[39] tested a series of thirty-nine allergic patients. In five patients, he reported positive reactions to skin tests and passive transfer test with these substances, whereas the standard extracts of these foods gave negative skin tests. These patients were all clinically sensitive to the foods in question. Cooke, therefore, according to Bloom and associates, arrived at the conclusion that clinical sensitization to protein digestion derivatives, at least at the proteose stage, does exist; and that, in some cases of food allergy, delayed clinical reactions can be explained on this basis. In such cases, skin tests with extracts of suitable preparations of artificially digested proteins give positive reactions. Blamoutier,[23] who studied a case of urticaria in which symptoms occurred approximately five to six hours after the ingestion of lamb, and lasted from twenty-four to thirty-six hours further substantiated Cooke's thesis. Cutaneous (scratch) tests with standard extracts with lamb meat were repeatedly negative. However, when lamb meat was incubated with the patient's gastric and duodenal juice in succession, the resultant substance gave a positive reaction on skin test and on passive transfer, whereas tests with gastric and duodenal juice alone were negative. Since a majority of the clinical reactions associated with negative skin tests are of a delayed type, these workers decided that their investigation should be concerned with the effect of digestion of foods on the antigenicity of such foods, as indicated by the skin test, by the correlation of skin test reactions with the results of intentional feeding trials, and the rapidity of occurrences of such clinical reactions. These investigators attempted to determine whether or not digestion altered the antigenicity of a food so that the resulting

complex was capable of producing a positive reaction on skin testing, which was not elicited by the unaltered food. If this occurred, they felt that the clinical reaction following the ingestion of the food should be of the delayed type, the delay theoretically being due to the lapse of time required for the production by digestion of the antigen to which the individual was sensitive and which was the actual cause of the clinical reaction.

That clinical symptoms can and do occur from foods yielding negative skin reactions is admitted by most observers. In many such instances, the reaction is of the delayed type, and they feel, that if it is due to food digestion, the delay should be equal to the period of time necessary for the food digestion and the production of a new antigen. The incidence of such delayed clinical reactions, due to food digestion, is not stated by other observers, but from the results of this study these clinicians are of the opinion that they are very few in number. Also from the results of this study, they believe that it is evident that the food digestion theory is not the explanation for the many cases of asthma, urticaria, rhinitis, or migraine with negative skin tests. Cases that can be proved to be due to specific sensitization to the products of food digestion in their experience appear to be limited in number.

Thirty patients with various allergic manifestations were tested with standard extracts and with the pepsin and trypsin digest extracts of ten common foods. Confirmatory clinical trials with the ten foods were made for each skin test, both positive and negative, by means of intentional feedings. The results of the skin tests with the standard extracts, compared with their pepsin and trypsin digest, are suggestive of changes in the antigenicity of foods due to digestion. However, Bloom and colleagues noted that out of the sixteen positive feeding tests clinical confirmation of a change in the antigenicity of foods due to digestion was obtained in only one instance wherein the standard extract failed to react in the skin, the digest extracts reacted positively, and the positive clinical reaction with the intentional feeding was of a delayed type. These investigators found that the results of this limited study suggest that the changes in the antigenicity of foods as a result of digestion, as indicated by skin tests and intentional feeding tests, are an infrequent occurrence. They concluded that in the search for the etiologic agent in nonreactive cases, the use of digest extracts for testing purposes will offer no advantage over a thorough and carefully taken history, confirmed by test feedings.

Bernton[20] reports that the effect of enzyme digestion upon the purified fraction of cottonseed-1A, the principal allergen from cottonseed, is significant. This allergen was subjected to the action of four crystalline enzymes: trypsin, chymotypsin, pepsin, and carboxypeptidase. (1) The allergen was digested by all of these enzymes. (2) Pepsin and carboxypeptidase, however, digested the allergenic fraction to a lesser degree than did trypsin or chymotrypsin. (3) Skin-reacting capacity was destroyed by trypsin, but not by pepsin or carboxypeptidase. (4) The peptic digest of the fraction was antigenic. The foregoing complexities of the subject of food allergy are increased by an analysis of the behavior of food allergens under certain conditions. A remarkable physical property of the allergenic protein fractions, CS-1A and CB-1A, isolated from the cottonseed and castor bean respectively, is their resistance to heat. For example, CS-1A, dissolved in water and autoclaved at 125° to 130° for an hour, gave positive cutaneous tests in the dilution 1:10. Clinical evidence will

now be presented to attest to the concept that the physicochemical characteristics of allergenic fractions not only vary from each other in different substances but vary from each other in the same substance. A patient of Bernton's was tested by the cutaneous method with an extract of celery. The reaction was strongly positive. The typical wheal with pseudopod formation was accompanied with considerable itching. The patient then exclaimed: "That is what happens to my lips when I eat raw celery. But I can eat cooked celery, as in soups, without any trouble." It is apparent that one allergen in celery is heat-labile in contradistinction to the heat stable allergens, CS-1A and CB-1A. This author cites the classic observations of Prausnitz and Kustner in their work on passive transfer as one of marked contrast. Kustner, it will be recalled, was fish-sensitive. Uncooked fish produced no allergic disturbances in him, but fish when cooked and subjected to a temperature of 55°C. became actively allergenic. In fact, cutaneous tests, positive with a boiled extract, provoked constitutional reactions. By way of supplement, the author cites another case history of a male patient, aged forty-two. Ever since he was a boy of seven, he could not eat fish either in the raw or cooked state. Extensive angioneurotic edema developed within five to ten minutes after ingestion. He could eat canned salmon or canned tuna fish however, without any untoward symptoms. This author therefore concludes from the foregoing clinical experience that multiple allergens in fish show a difference in susceptibility to temperature changes. Some are active in the fresh state, some are activated by a temperature of 55°C., and all are inactivated by the temperature of the canning process.

FOOD CONTAMINANTS

Randolph[140] wrote that since food allergy had not yet been completely described or adequately differentiated from intolerance to various chemical contaminants employed in food manufacture, he was trying to do this. It was his feeling that chemical contaminants of common foods were capable of giving allergic-type reactions in certain patients who are intolerant to these exposures. At first glance, these patients might be regarded as being food-sensitive. He points out that this may be a much bigger problem than it first appeared, so common is the technological chemical contamination of foods and so frequent is this clinical problem of intolerance to a wide range of petro-sulfo-chloro and other halogenated chemical exposures. For example, the author explained that he had always been puzzled by the rather common existence of so-called multiple fruit sensitivity, which seemed to involve selective fruits, relatively independent of their botanical families. He felt that this might be a reaction to a common factor or fruit technology, as these reactions occurred principally in patients with other manifestations of intolerance to diverse synthetic chemicals. This investigator cites an incidence occurring in the summer of 1953 when three such patients were tested with unsprayed and unsulfured peaches. Each patient was said to have been highly allergic to peaches, facts demonstrated when these individuals were fed commercially available peaches under observation. But the same patients tolerated unsprayed, unsulfured, unfumigated and "wormy" peaches. These tests were also done blindly, unless the presence of an occasional worm hole might be said to have interfered with their objectivity. Whole unpeeled peaches were used in both instances. In another incidence in 1954, similar tests were run on fifteen patients who were said to have been peach sensitive, but only three were actually sensitive to uncontaminated peaches, as de-

termined by the ability to develop sharp clinical reactions when these were fed experimentally. Peaches dusted with sulfur as a fungicidal agent caused severe reactions in several, as also did unsulfured peaches from an experimental horticultural lot, sprayed on a known and recommended schedule with DDT and parathione in an oil vehicle. In some instances, allergic type reactions were so intense that patients refused to submit to further testing. As a result, this series is not complete. But as several patients reacted to each type of contamination, it suggested that there is something in both the sulfured peaches as well as in those treated with chlorinated hydrocarbon-oil mixtures that precipitated acute allergic type reactions; whether it is the active ingredient of the spray or the oil vehicle cannot be said at present. The same type of response has been observed in other patients in this current season. This author contends that the same holds true for tolerance to unfumigated dates and figs, whereas dates and figs fumigated with methyl bromide (the customary commercial practice) results in the production of a severe reaction in certain of those allergic individuals having other aspects of this petro-chemical story.

As pointed out by Feinberg,[59] the incidence and seriousness of allergy to drugs of known identity are sufficiently important to deserve attention in their own right. But to this must be added the possibility that in addition to this allergy to labelled drugs and chemicals many persons may experience acute or chronic allergy from other just as simple chemicals present in food, in the air, and perhaps intrinsically; these cannot be labelled at the present time. He found that in about one third of the chronic asthma patients and about one half of those with vasomotor rhinitis, no allergy or infection could be identified. In the majority of instances of protracted urticaria, allergic causes were either known simple chemicals (aspirin, phenolphalein, sulfonamides, penicillin) or they could not be identified. May it not be possible that these also are the types of people who have unfortunately developed an allergy to simple chemicals rather than to proteins? If they take the chemical (drug) from a bottle labelled "aspirin" or "sulfathiazole" and get asthma or hives, they know to what they are allergic, even though these substances will not give a positive skin test. But if they are allergic to just as simple a chemical in the food or in the air, the cause is not identified. Incidentally, it is not beyond the realm of probability that the Penicillium spores in the air or Penicillium mold in foods or even other mold products might be the cause of some obscure cases of allergy comparable to those produced by penicillin administered for therapeutic purposes, according to Feinberg.

It has been demonstrated clinically that both human and cow's milk may be contaminated with various allergens. Pinto[138] has noted sulfanilamide and acetylsulfanilamide in human milk. Rosen[168] has reported penicillin in milk. Luisada[110] observed favism occurring in infants, the source of the fava bean antigen being traced to the mother's or goat's milk. Numerous other substances, both chemical and foods, which were included in this diet of cows or lactating mothers have caused allergic reactions.[33,148]

As reported elsewhere in this review, Tuft and colleagues[209] observed an interesting case in the person of a young chemist with nasal and cerebral symptoms of allergy, proven by clinical study to be sensitive to skin-test-negative foods high in sulfur content. He was especially sensitive to egg and less so to peanut, molded cheeses (not cottage or American), raw garlic, onion and corn. When these foods were eliminated from the patient's diet he was symptom free. During the course of these investigations and in attempting to explain the clinical reactions of the ingested

food in the absence of positive skin tests, the patient suggested the possibility of a correlation between the sulfur content of the foods and their tendency to provoke symptoms. The patient was then tested by the ingestion of capsules containing methionine and later cystine. Following the ingestion of the sulfur-containing-amino-acid with methionine (a substance which is also present in eggs and the other foods listed above), a similar set of allergic symptoms occurred. Since methionine is related to and, in fact, may be converted to cystine, it is possible that allergy existed either to both or to their end-products. Since amino-acids like methionine do not give positive skin-test reactions even in allergic patients, determination of sensitivity to them by routine skin-test methods obviously is not possible and can be elicited by clinical methods alone. It was found that 1 gm of methionine taken three times daily produced the same symptoms as resulted from ingestion of four eggs. Lesser symptoms could be produced by cystine. That the reaction might be biochemical rather than immunologic was suggested by these investigators because of the suppression of the clinical reaction to egg ingestion during a twenty-day period of aureomycin administration given to eliminate the normal intestinal flora.

Figley and Rawling[61] studied the problem of castor bean dust's contaminating green coffee. Their patients were exposed to dust from burlap coffee bags which had at one time contained, or had been contaminated by, castor beans. All patients were sensitive to the castor bean dust and some were also sensitive to green coffee bean dust. Even those sensitive to the coffee bean dust could drink coffee without symptoms. These investigators found that the green coffee bean contained an important allergenic fraction that following extraction is heat stable. Extract of roasted coffee, however, gave a negative reaction, showing that the roasting process successfully destroys the allergenic fraction of the green coffee bean. Coulson and his co-workers[43] extended these observations with further studies, and their results imply that contamination of green coffee with castor bean is not exceptional. They further pointed out that the hazards resulting from the contamination of green coffee with a castor bean derivative are significant only to those who are exposed to green coffee.

Various water-soluble vegetable gums used as fillers in foods or as emulsifiers, stabilizers or adhesive agents in numerous pharmaceutical and cosmetic preparations have been shown to be allergenic. The principal gums and their sources are gum acacia (syn. gum arabic) derived from Acacia senegal, karaya gum (syn. Indian gum) derived from Sterculia urens, and gum tragacanth derived from Astragalus gummnifer.[217] Ouer[133] reported an investigation of the sensitizing properties of another vegetable gum, Kelcoloid, which is extracted from giant kelp, Macrocystis pyrifera. He found positive skin reactions in five out of fifty allergic persons, and three of the five showed mild clinical sensitivity on ingestion of large amounts of Kelcoloid. No positive reactions occurred in fifty nonallergic persons. Ouer concludes that Kelcoloid has low allergenicity and would be a satisfactory substitute for other water-soluble gums. Brown and Crepea[28] reported a case of sensitivity to gum tragacanth in which the offending agent was found to be in 5 mg amounts in a tablet of pyribenzamine. Severe symptoms of asthma and urticaria were caused in this patient by this small amount. The authors believe that in view of the wide usage of the different gums, these allergens should be used more often in routine testing.

Sheldon and Yorke[185a] presented an interesting case of a housewife, aged fifty, with no family or personal history of allergy who had

suffered with a rather severe eczema associated with anorexia and mental depression since 1940. These investigators have shown that the patient's symptoms were directly due to the consumption of bread or flour which contained either nitrogen trichloride (agene) or chlorine dioxide. It was clearly demonstrated repeatedly by clinical trial that this patient was sensitized to the chemically treated flour the same as some people are sensitive to some medicines or chemical contaminants of food as the symptoms cleared when she used bread made by a special aeration of processed flour which, of course, was not treated with these chemicals.

METHODS OF SKIN TESTING

Walzer[224] contends that an appreciation of many of the valuable diagnostic procedures may be lost to the physician through their injudicious use. He explained that there are many points to be considered in order to evaluate the comparative merits and disadvantages of the scratch and intracutaneous tests. The intracutaneous test is considered to have greater diagnostic potentialities. On the other hand, it is dangerous in inexperienced hands. This clinician warns that the expert has learned to prevent constitutional reactions, but such dangers are still formidable for the novice who would be well advised to restrict himself to the use of the scratch technique. Lest the unwary be misled by the irresponsible assurances that intracutaneous tests with an allergen are "safe" if a preliminary scratch test with the same allergen is negative, it should be pointed out that even such a precaution is not foolproof when the testing materials employed for the scratch tests are not dependable. Walzer states that no technique is better than the technician who uses it. The diagnostic value of the techniques will depend more on the clinician's ability to interpret his results correctly than on the elicitation of positive reactions. Both the scratch and intracutaneous tests will prove valuable to any worker who will take the time and effort to study and understand the procedure and materials which he is using. Tests with pooled allergens in the form of "group" tests are neither time-saving nor trustworthy. One irritating extract in the group may falsely implicate all of its component allergens. A positive reaction necessitates separate tests with all members in the group. Group testing merely multiplies the pitfalls which are encountered in testing with individual allergens.

There are many methods used to break the skin previous to the application of a test allergen. Von Pirquet used a scarifier. It is an instrument similar to a small screw driver which is whirled or rotated rapidly between the thumb and forefinger to scarify or denude the skin. According to Harley,[77] the prick method of skin testing was introduced by Lewis[104] in his classical studies of the reaction of the skin to histamine, as the most suitable method for exact quantitative results. It was first applied by Freeman[64] to the diagnostic skin testing of an allergic patient. He writes that for the routine clinical use the advantages of the prick test over the more commonly used scratch and intradermal methods are the simplicity, accuracy, almost complete absence of discomfort to the patient and rapidity of performance—the latter a very important point when dealing with children and with large numbers of patients in the clinic. He contends that doubtful and false positive reactions are much less frequent than by scratch or intradermal methods because the amount of trauma inflicted on the skin by the prick test is much less and more constant in degree. Also the risk of general reactions, by no means negligible with the intradermal and scratch methods, is practically nil with the

prick test. Although the size of the reaction is smaller than that of the scratch reaction, the prick method gives more uniform results, as shown by carrying out the test in duplicate or triplicate on comparable areas of the skin and. except in dermographic skin, non-specific reactions are rare, because of the very minute amount of test fluid deposited in the cutis vera. The technique of prick testing is given in detail in the article.

Included in a questionnaire concerning sensitization as applied to skin-test reactions, Tuft and Heck[210] endeavored to find out just what technique was used by most practicing allergists. Of the 310 physicians who replied, 58.7 per cent used a combination of scratch and intracutaneous methods; 36.4 per cent used intracutaneous alone; whereas a comparatively few used either the scratch test alone (2.3 per cent), or the puncture or prick test combined with intracutaneous (2.6 per cent). In the scratch and intracutaneous methods groups, a statement was usually made that the scratch test was generally used first, and that all negatives were retested by the intracutaneous method. In a few instances, it was stated that the scratch method was used only where a definite clinical history of severe reactions was obtained, but otherwise patients were tested by the intracutaneous method. Among the numerous comments made, further emphasizing the natural interest these physicians have in the subject of skin testing, was that concerning the necessity for improvement both in the testing methods and more particularly in methods of standardization. They also commented upon the variability in the testing material and the need for properly standardized, potent, and reliable extracts. Some criticism was directed against the technically unreliable extracts. Some criticism was directed against the technical inaccuracy of tests done, especially by untrained or improperly trained workers using irritating extracts or injecting too large amounts (0.05 or 0.1 ml) when doing intracutaneous tests.

Precision scratch testing with a micro-scratcher has been done in the allergy clinic at the University of Kansas Medical Center for the past five years. This instrument, which was devised by Morrison,[122] has been used routinely as a means of scarifying the skin before applying the scratch test allergens. According to this writer, the instrument has aided the supervised novice in painlessly applying the epidermis abrasions of consistently uniform depth and length. It also produces a true scratch, or possibly more nearly, a cut which appears as a white circular or heart-shaped line. Excellent whealing reactions result whether the allergens applied immediately or an hour or more after the skin is scratched. Although this instrument was not originally intended to produce painless abrasions, this unexpected feature has greatly enhanced its usefulness, especially in the tasks of testing children. Adults, who have been tested previously by conventional methods, have expressed their appreciation of this feature. About fifteen or twenty scratches can be performed a minute, and these can be applied in clear-cut and persistent pressure rings are desirable. A hurried technique loses advantage of this feature; it is necessary to make several scratches of different depths before choosing the depth setting most suited to the individual skin. Experience may diminish but will not eliminate the need for such preliminary testing. The simple technique and a picture instrument are included in the article.

When skin testing of the patient is unpractical or impossible because of cutaneous disease, severe illness, or other complications, the indirect (passive transfer) method is indicated according to Walzer.[224] He states that by introducing small amounts of the patient's serum into cutaneous

sites on a normal substitute, sensitized areas are created which may be tested intracutaneously after a few days for sensitivity. Each test is controlled by a similar test on the neighboring unsensitized skin. An excess of reaction at the sensitized site over the control represents a positive reaction. This excellent control (which has no equivalent in direct testing) is one of the greatest assets of the passive transfer technique. He warns that the indirect method of testing is an involved procedure which requires considerable experience for its effective performance.

Shulman[181] reports on ophthalmic testing with food allergens as compared with the commonly employed cutaneous methods in an attempt to evaluate the ophthalmic test. Although there are in the literature a number of reports regarding ophthalmic tests in inhalant sensitivity[1,31,136] this report is probably the only one regarding ophthalmic testing to food allergens. According to this investigator, the dry food allergens were especially prepared in a nonirritating ophthalmic ointment and in a concentration of 1:10 by weight. Twenty-one different food allergens were used in this experiment. The ophthalmic reactions occurred from twenty minutes after instillation up to twelve hours. A marked injection of the sclera was recorded as a positive reaction. The author found that repeated tests with the same allergen gave constant results, and in no case was sensitization of the eye noted. When ophthalmic reactions were compared with the skin reactions, it was noted that in many cases negative ophthalmic reactions occurred despite the presence of large skin reactions and vice versa. In 814 ophthalmic tests, an attempt was made to determine the clinical significance of the suspected food. This author states that probably the most valid comparison between the eye and skin test can be made if the clinically negative patients are regarded as a "control group." The percentage of positive reactions is then regarded among this group as a measure of the naturally occurring number of positive reactions; therefore, subtract this per cent of positive reactions in the clinically positive group thus using the difference obtained as a measure of the sensitivity of the test. This, he contends, is in effect an over-all measure of the combined effectiveness of the test in both reporting true allergy and not reporting false alarms. (This per cent varies from 100 for a perfect score to 0 for complete nondiscrimination.) He concludes that the percentages thus obtained are 7.3 per cent for the skin test, and 86.8 per cent for the eye test, showing very well the great superiority of the eye test. In all groups sufficiently large to permit a valid statistical conclusion, the eye showed itself superior both in detecting an allergic condition and in not reporting "false alarm" on a clinically negative patient.

The introduction of chemical materials into the skin by means of a galvanic current has been practiced for many years and with many substances according to Morse.[123] Following the work of Abramson[4,5] and also of Dutton[53] in skin testing by electrophoresis, an apparatus was devised by Morse which enabled him to apply simultaneous application of as many as sixty-six allergens. The apparatus, according to this investigator, consists of an active electrode, an indifferent electrode, and a simple galvanic current apparatus, using as a source of current two 45-volt "B" batteries, equipped with a milliampere meter. For further description of the apparatus and the methods of use, the reader is referred to the author's original article. He contends that the method is entirely without discomfort and, therefore, is particularly helpful in

testing small children. In practice, constitutional reactions have never been observed in spite of the occurrence of many strongly positive reactions. He found that while the aqueous extracts penetrate the skin more readily, glycerinated pollen extracts have proved satisfactory. Positive reactions have been obtained with dust, silk, and other inhalants, and with numerous food extracts, but the author feels that food extracts have not been sufficiently concentrated to give dependable results by this method.

CLINICAL VALUE OF SKIN TESTS

Matheson's[114] brief review of the history of skin testing is interesting. He credits Blackley[22] with first using the skin test as a diagnostic procedure in pollinosis. Blackley's work was repeated and verified by many individuals, but it was not until von Pirquet popularized the skin test for tuberculosis in 1907 that attention was focused on the method as a diagnostic aid in allergic diseases. According to this author, Smith[189] and Schmidt,[184] in 1910, used the scratch technique in the diagnosis of food allergy. However, it was Schloss[183] in 1912 who, after much experimentation, systematized the scratch technique as an aid in the diagnosis of this condition. In 1914, Goodale[73] advocated systematic use of the scratch test for diagnosing hay fever, and Cooke[40] about the same time, encouraged by the work of Schick on the intradermal test with diphtheria toxin, published his work on the intradermal test in the diagnosis of allergic disease. Then followed the controversy on the relative merits of the scratch versus the intradermal test, which remains to the present day.

For several years, many papers have been published and there has been much discussion on the value as well as the comparative value of scratch and intracutaneous tests. There is a decided difference of opinion[7,90,130,150,196,198] regarding the relative merits of the scratch and intracutaneous tests as indicated by Narins.[127] The data he presented following a series of skin tests demonstrated that in atopic dermatitis the results of scratch tests carried out at weekly intervals with the same allergen in the same region of the skin showed variations ranging from negative to definitely positive. Also in atopic dermatitis, the results of scratch tests carried out simultaneously on two symmetrically situated skin sites in the same individual and repeated at weekly intervals showed variations ranging from negative to definitely positive, both from site to site and from week to week, and these variations occurred regardless of whether the powdered or the glycerinated extracts were used. This investigator found that in a series of cases of atopic dermatitis, two intracutaneous tests with the same allergen were carried out simultaneously in symmetrical sites in the same individual. At the same time, and in the same individual, two symmetrically situated scratch tests were performed with the same allergen. Whereas the simultaneously performed intracutaneous tests always showed approximately equal reactions, the simultaneously performed scratch tests differed widely in the reaction elicited. He has also noted that similarly, when scratch tests were compared with intracutaneous tests in case of non-cutaneous atopic disease (hay fever, asthma) variable or completely negative results were produced with the scratch test; whereas consistently positive results were produced with the intracutaneous tests with the same allergens. He infers from these results that the reactions to scratch tests, even when performed in the same individuals at the same time in symmetrical sites, vary so widely in degree that their usefulness as a guide to existing

skin hypersensitivities of urticarial type must be much inferior to the result of the more constant intracutaneous method. However, he suggests, as stated by the previous authors cited above, that each method presents certain advantages of relative safety, availability of test materials, ease of application and economy. He believes that the results achieved with the extracts used have too often been unreliable.

Hill[83] studied 100 asthmatic children between the ages of three and twelve years. In almost all, there were periods of at least three or four weeks of freedom from wheezing. These patients were tested by the scratch method and their symptoms observed. Thirty-five gave one or more positive tests to foods, and sixty-five gave none. This investigator recognized the fact that an intracutaneous test to a food is often positive when the scratch test is negative. It was formerly his custom to do a routine intracutaneous test with foods in all asthmatic children until he noted that there were so many positive reactions that meant nothing clinically and that he rarely obtained any valuable information, so this procedure was given up. He is quick to suggest, however, that in the environmental allergens the intracutaneous tests are of great value and, when positive, usually indicate clinical sensitivity even when the scratch tests are negative. There were 218 positive scratch tests to foods in the 100 children tested. Of these, there were forty-four (20 per cent) in which it was definitely proved that the food in question could cause asthma. It is interesting to note that egg white, fish, peanut, walnut and chocolate accounted for thirty-eight of the forty-four etiologic tests. Although in his hands potato gave twenty-two positive tests (some of them large wheals with pseudopods), in no case could it be shown that the ingestion of potato induced asthma or any other symptom. On the other hand, spinach was the cause of asthma in one patient but spinach gave a large number of positive skin tests because of its nonspecifically irritating quality. No symptoms resulted from the 158 foods (72 per cent) to which test showed skin sensitivity. This investigator contends, however, that it is probably true that asthma would have been produced in some of these patients had a considerable amount of the food been ingested. Not uncommonly, the degree of sensitivity to some of these foods, such as fish and nuts, is so high that as soon as any of the foods touches the lips or enters the mouth, the mucous membrane begins to swell, and the food is immediately spat out or regurgitated before it has been absorbed. If these cases are included, the number of foods producing asthma has increased from forty-four to sixty. Hill concludes that in this series about a fifth of positive scratch tests to foods in asthmatic children were of etiologic significance.

Despite certain drawbacks and disadvantages, allergy skin tests are still the most important and most widely used method of diagnosis employed in allergic diseases. Tuft and Heck[210] are quite right in stating that while differences in application or in technique exist, nevertheless most allergy patients seen by either the practicing physician or the allergy specialist have some form of skin tests performed upon them as a part of the diagnostic study. Following the performance of such tests, the resultant reactions are recorded and reported. Whenever possible, attempts are made to determine whether the positive reactions are of clinical significance (a clinical positive) either by correlation with the patient's clinical history or by some form of clinical trial. Despite differences of opinion expressed by many authors as to the need or desirability of doing skin tests, especially in patients with clinical manifestations of food

allergy, skin-testing methods nevertheless can be and often are of considerable aid in the management of allergic patients and are widely utilized for that purpose.

During the course of daily allergy practice, the question sometimes is raised as to whether skin test reactions change either spontaneously or perhaps as the result either of abstinence or of treatment. Thus, for example, the physician sometimes is asked by patients who have eliminated positive-reacting foods for varying periods if they can be retested to determine whether or not these foods can be added again to the diet safely. They have the idea, often shared in or even suggested by the attending allergist, that improvement in their tolerance for that food should be demonstrated or accompanied by a decrease in the size of the skin reaction and, therefore, retests can be utilized as a means of detecting the improved tolerance. As shown from analysis of the data from 310 practicing allergists and as indicated by their critical review of the literature, these investigators have reported that there is a divided opinion as to whether the skin test reactions change and also as to the reason for such a change. As a result of their study, these clinicians believed that the following conclusions seemed justified: (1) Patients can and do acquire sensitization to new food allergens. This tendency is enhanced by continued or prolonged contact with these agents since sensitization as indicated by positive skin test reactions occurred more frequently in relation to commonly eaten foods than to those uncommonly eaten. (2) Once skin sensitization occurs, as evidenced by a specific positive skin test reaction, it changes very little either as the result of allergen avoidance or of treatment. Thus avoidance of foods for varying periods of time as well as specific pollen therapy as a rule produced little or no significant change, except, as in the case of pollens, after long-continued treatment (five or more years). Therefore, one should not rely upon a reduction in skin-test reaction as a criterion of improved tolerance to permit re-addition of a food or as a guide in pollen therapy. (3) Skin test reactions may change with advancing age, especially after fifty, because of a lessening of skin reactivity. These authors point out that the results of their studies would also suggest another point which might be applied profitably in clinical practice. Since the incidence of positive skin-test reactions to foods infrequently eaten is quite low, their elimination from the routine skin-test lists would seem advisable and as desired by allergists, for it would serve to increase the value of, and respect for, our testing methods. It would also shorten the testing procedure materially.

Kremer[96] suggests that intradermal tests are more trustworthy than the scratch test, but even though this is admitted there are many who consider that skin tests of foods are of little value because only a small percentage of the tests can be correlated clinically. This investigator concludes that one reason for, or one possible cause of, the variability of the skin reactions with food extracts is the fact that when food is omitted from the diet, the patient not only tends to lose clinical sensitivity but that his skin test also will gradually become negative. He suggests, further, that when the patient uses the food again, the skin tests will again become positive. In the case where the skin reaction is slightly positive and there is some doubt as to its interpretation, the patient should be instructed either to avoid the food completely or to add the food to the diet, and then the tests would become either definitely positive or definitely negative. This author cites several clinically controlled feeding tests and skin reactions to prove his contentions and concludes that

the intracutaneous skin tests to foods are highly important and accurate.

One of the difficulties which plague the allergist in his efforts to detect causative agents by diagnostic skin test methods is the negative skin test reaction to foods or drugs which nevertheless induce definite and recognizable clinical symptoms. One explanation for this failure, according to Tuft and his co-workers,[209] is that the allergy exists in relation to such split products as proteoses, peptones or amino-acids rather than to the whole protein itself. Since these split products do not give specific skin-test reactions even in susceptible subjects, diagnosis of this type of allergy depends solely upon the clinical history, which makes it difficult to obtain evidence indicating that they are causative factors. These investigators report, that while some isolated instances have been reported in the literature,[39,147] even these data have not been conclusive. The authors report a study of a patient who apparently reacted abnormally to certain split products, as indicated by the results of their clinical investigations. They found that in a patient with nasal and cerebral symptoms of allergy, proven by clinical study to be due to sensitivity to skin-test-negative foods high in sulfur content, especially egg, clinical and experimental studies showed that identical symptoms could be produced repeatedly by the ingestion of methionine, a sulfur-containing amino-acid which is present in large amounts in egg and other foods. They believed that the clinical reaction to the ingestion of egg during a twenty-day period of antibiotic administration, given to suppress the normal intestinal flora, indicated that the reaction might be biochemical rather than immunological. However, they conclude that regardless of the basic cause, the demonstration of an abnormal reaction to protein split products (in this case an amino-acid) might help to explain those instances of food allergy with positive clinical histories and negative skin reactions.

Reliability, therefore, the importance of skin tests with foods is questioned by Leibowitz and his colleagues.[100] In fact, they contend that the value of food tests in the management of allergic patients is being questioned by many leading allergists. The basic principle of the diagnosis of the specific etiological agent is involved. If skin tests with food extracts are not reliable in the diagnosis of the etiological factor, then the procedure is questionable. Indeed, Randolph[141] and Rowe[172] do not depend on skin tests for determining the etiologic significance to foods, and Hill[83] and Unger[216] have stated that the intracutaneous method of testing yields many positive reactions which are without clinical significance. In studying a group of seventy patients with respiratory allergies, thirty-four children and thirty-six adults, these clinicians used the intentional feeding tests to obtain clinical conformation of the results of 2,467 skin tests, of the total of 3,920 skin tests with foods studied. Of the 3,920 skin tests performed, 1,732 (44.2 per cent) were positive; the positive responses included slight reactions, which comprised 80 per cent of these positive tests. These investigators found no relationship between the frequency of the positive skin reaction and the positive clinical trial with the individual foods tested. Fish and nuts yielded the highest number of negative skin tests but resulted in the greatest number of positive clinical trials when the skin test was negative. Wheat, milk and egg were not of etiological significance in this study, either by direct skin test or by clinical trial. They found that positive intentional feeding tests were obtained in twenty-eight (40 per cent) of the group of seventy patients studied; these included foods causing either positive

or negative skin tests, and these confirmations occurred in twice as many children as adults. In 35 per cent of all patients, the positive food skin test was confirmed clinically. It is of interest to note that the low incidence (1.9 per cent) of positive clinical trials with foods that were negative with the intradermal skin test confirms the reliability of the negative skin test. Leibowitz and co-workers conclude that the clinical confirmation of the foods giving positive intradermal skin tests in 35 per cent of the patients studied indicates that skin tests with foods is a useful diagnostic procedure and should not be abandoned regardless of the fact that food may play a minor role to pollens, inhalants and bacterial allergy in the majority of the respiratory allergy cases they studied.

In answering the question as to whether or not skin tests change, Matheson[114] pointed out that it is common knowledge among allergists that positive tests to foods may readily become negative if contact with these foods is avoided for a variable period. Positive skin tests to such foods in infants or young children frequently become negative before the age of seven years and sometimes sooner, except in cases of violent skin sensitivity which results from such allergens as fish and nuts. On the other hand, it has been his experience that skin sensitivity to inhalants, such as animal dander, house dust, pollen and others, practically never disappears regardless of avoidance of contact or hyposensitization.

Tuft and his co-workers,[212] in previous reports, indicated that changes in skin test reactions may be due to a physiologic loss of skin reactivity concomitant with advancing age. To ascertain this, these investigators first tried to determine the incidence of positive skin reactions at various decades of life by review of sufficient skin-test records of private patients to provide 100 for each food and for each decade of life. In addition, intracutaneous tests with four concentrations of histamine (1-1000, 1, 1-10,000, 1-100,000, and 1-1,000,000) were done upon nonallergic persons, testing 100 in each decade of life. The results of these investigations showed the following: (1) The incidence of positive skin test reactions to food allergens is highest in the first decade of life. It decreases slightly up to age fifty, but after fifty (and especially after sixty), it decreases sharply, especially compared with the first decade. (2) According to the histamine tests, skin reactivity is highest in the first decade. It diminishes slightly from the second to the fifth decades, and markedly after the age of sixty. (3) Failure to demonstrate positive reactions in older persons may be due to loss in skin reactivity rather than to a lack of specific sensitiveness. These authors contend that their studies suggest the possible utilization of histamine skin tests (1-10,000 and 1-100,000) concentration as a means of determining skin reactivity.

Hill[83] found that in 218 cases of positive tests in the series of 100 children studied, the corresponding food could be eaten with complete impunity in 158—there was no asthma, urticaria or eczema, in spite of the fact that in many of these patients the skin showed a high degree of sensitization. This clinician contended that some of the postive tests have been of etiologic significance when the child was younger, and with increasing age he had become "tolerant" to the food; some of them had never been of etiologic significance. There is a great tendency in allergic children to acquire tolerance to foods as they grow older; many children who have violent symptoms from egg white at the age of a year can eat it with impunity at the age of six years, but the positive skin test often persists, and the reaction may be as large as it was in

the beginning, according to this author. Tolerance to environmental allergens does not come so readily: the child clinically sensitive to cat hair or to ragweed pollen is likely to remain sensitive for a long time, often through life.

Matheson[4] points out that since the scratch tests have been introduced, they have been popularized by physicians in diagnosing allergic disease. Publicity has aided in a misconception, however, of their value in diagnosis, not only among some professionals, but particularly among lay people. Matheson comments that there is little doubt that skin testing is an aid in the diagnosis of allergic disease, but, like some other laboratory procedures, it must be properly interpreted and evaluated. He emphasizes the fact that no one should ever resort to skin testing as a routine procedure before careful history and physical examination. On occasions, he has been presented with reports from skin-testing laboratories of numerous positive skin tests to foods, as a result of which many foods were omitted from the diet with harmful results on the growth and development of children. Closer study invariably revealed that positive skin tests to the foods had nothing whatsoever to do with the etiology of the presenting complaint, and in many instances these tests were not positive when repeated. He rightly contends that it is unfortunate that laymen have been educated to the belief that skin tests are in themselves diagnostic, and so, in many instances, employ technicians to perform these tests before taking the child to a competent physician. On the other hand, there has been a tendency among certain physicians in the past several years to belittle the value of skin tests in general and particularly to foods. While no one can deny the value of elimination diets, intentional feedings and environmental control, each of which has its limitations, particularly when applied to children, in a similar vein, one should not neglect skin testing, which is not only a helpful but also a comparatively simple procedure. He states that the physician is often discouraged with skin testing because of the frequent negative responses with allergens he expects to give positive tests. Sometimes it is the child's skin that is blamed for being nonreactive, or sometimes the physician blames the allergen as not being potent. However, in many instances, closer study will reveal that neither is a true explanation; the child's skin is anergic, a condition which exists in approximately 3 to 5 per cent of children. However, this investigator contends that in general the skin of infants and children is fully capable of demonstrating an antigen-antibody reaction in the form of erythema, with or without whealing, depending on the concentration of antibody present in the skin and the potency of the antigen introduced.

Matheson has observed that it is not the age of the infant, but the clinical type of the allergic condition under consideration and the presence or absence of antibodies in the skin as well as the potency of the allergenic extract used for the test that are the determining factors. This author states that strongly positive whealing skin reactions to egg white are common in very young allergic infants, particularly when eczema is present. Similarly, it is not unusual to obtain positive skin tests to milk and wheat and, after the first several months of life to various inhalants as well. In older children, the association of positive skin tests to foods, with clinical symptomatology, has the same status as in adults. About 50 per cent of such positive skin tests merely indicate past or nonspecific sensitization and are not responsible for clinical complaints. Negative skin tests to foods do not by any means rule out their clinical significance.

However, in his experience such foods as lettuce, tomatoes and spinach frequently produce positive skin tests, but seldom are responsible for allergic symptoms. For these reasons, there is much controversy as to the value of skin testing to foods in the older child or adult, and Randolph[141] and others have completely relied on history, elimination diets and intentional feeding as diagnostic methods. According to this author, a positive skin test to food in the young infant is of much greater clinical significance than in the older child or adult. And in his experience, foods are more likely to play a significant rôle in atopic dermatitis, urticaria and gastrointestinal disturbances than in respiratory allergy.

Squier[192] rightly contends that patients often are referred to allergists by physicians who assume that simply by doing a series of skin tests the allergy problem can be solved and an etiologic diagnosis provided. It has been said so often that Squier felt repetition seemed almost trite, that skin tests contribute only bits of evidence in an allergic study and must be correlated with all other findings to establish the etiologic diagnosis. The results of skin tests with foods, regardless of potency of antigens and accuracy of testing, are more difficult to correlate with specific clinical sensitivities than are the results of similar tests made with inhalant allergens. The inhalant allergen enters the blood stream essentially in its intact form. When sensitivity develops, the unchanged protein material in the inhalant is a specific antigen, and potent extracts for skin testing can be made with relative ease. This is not true for foods, where sensitivity often develops to one or more split protein fractions. Testing extracts, as used, are prepared from intact foods. For this reason, some allergists believe that skin tests with foods give little or no information of value. However, such tests do indicate, in a rough fashion, the spectrum of skin sensitivity in the patient. For example, one frequently sees a number of reactions occurring to food antigens belonging in a genetically related group, and the knowledge of these reactions is helpful in planning subsequent clinical trials.

Squier concludes that positive skin reactions to most foods are laboratory results and are helpful clues to assist in the recognition of possible causes of clinical food allergy. It is still important, however, to emphasize that these tests are only clues, and the fallacy of listing all food extracts which caused skin reactions and giving the list to the patient for subsequent guidance should be obvious. An even more reprehensible practice, he contends (and we agree) is to give patients lists of food reactions with written instructions that positive reacting foods should be eliminated to the relative extent indicated by the recorded plus marks for the degree of skin sensitivity to the skin tests to those foods.

The reviewers recently saw a patient who had been skin tested and handed a list showing foods to which he was skin sensitive. He was advised to eliminate the four plus foods for one week and, if not improved, then to eliminate the three plus for one week, next the two plus, and finally the one plus foods. He remarked that the "nurse-tester" failed to advise him further, and the physician was too busy to see him.

In reviewing the meaning of skin tests in allergy, Samter[181] suggests that if diagnostic procedure had to be selected which was representative of the practice of allergy, then skin tests would be the logical choice. Skin tests, that is the immediate type, have enhanced our understanding of the relationship between sensitization and clinical symptoms of the allergic individual. When skin tests are used as a primary diagnostic

tool, and as a sole basis for treatment, then they can be responsible for many therapeutic failures. There is a satisfactory correlation between positive skin tests and clinical symptoms of the most common respiratory allergies such as seasonal hay fever and bronchial asthma. In allergies to environmental inhalants, the percentage decreases sharply, while in allergies to food the correlation is practically non-existent. For example, it is almost impossible to detect a sensitivity to strawberries by testing patients with strawberry extracts. The reason for this discrepancy is not yet clear. In food allergy, the lack of correlation might not be due to the uneven distribution of antibodies, but due to the fact that the methods of extraction might have destroyed some of the characteristics of the allergen; that is, the use of inadequate testing material. This investigator states that a study of the reasons for the absence of skin reactions to foods in established food allergy must be, and is, part of current research in allergy, but it is important to acknowledge this absence as part of the diagnostic difficulties.

He states that the policy of the positive skin tests is responsible for a considerably larger number of incorrect diagnoses in allergy than the policy of the negative tests. Most physicians, according to this author, prefer not to perform their own skin tests, which require the maintenance of perishable material and rather elaborate equipment. He maintains that in many cases that have come to his attention, patients, particularly children, have been sent to laboratories which specialize in the performance of skin tests; this is an acceptable procedure if interpretation and subsequent treatment are left to the referring physician. However, some laboratories not only apply the tests but at the end of the examination issue a comprehensive booklet, suggesting that the patient avoid inhalants and foods which have produced positive skin reactions. As a result he has seen a sufficient number of children on unnecessary and deficient diets to state that this practice disregards the progress which diagnosis and therapy have made during the past decade; furthermore that the technique is particularly pernicious if it pertains to foods, because once a patient has been told that he is allergic to food he will correlate some of his functional responses with the foods that he has eaten. All people eat. The author rightly suggests that most people suffer occasionally from headaches, indigestion, fatigue. Once these two facts have been linked, it is difficult indeed to separate them. He suggests that if one must test patients to foods, it is better not to inform them of the nature of any positive tests until a subsequent day-by-day diary has confirmed their clinical relevancy.

The author reports on a very interesting experiment conducted several years ago, in which the etiologic diagnosis made only on the basis of skin tests in one group of patients was compared with another group in which the etiologic diagnosis was made only on the history, or on the basis of the interviews with the patient. With this procedure he reports that an approximate diagnosis was made in less than 10 per cent of the patients of the first group that was skin tested, and an adequate diagnosis was arrived at in almost 70 per cent of the patients of the second group. He contends that these figures, which so strongly favor the history as a primary diagnostic tool in the type of allergic conditions under investigation, speak for themselves.

Samter has confidence that a conservative attitude which integrates skin tests into the wider horizon of the allergic survey will not only safeguard their status as an important, if secondary, diagnostic procedure,

but will add to their usefulness in the control of the increasing problem of managing diseases of sensitization.

In commenting on the clinical value of skin tests in allergic conditions, Pearson[135] suggests that skin tests do not provide a shortcut to speedy diagnosis, and in the hands of those who expect too much they are often misleading. It is true they often demonstrate the presence of antigen-antibody mechanism but it is not necessarily associated with symptoms in every case in which it is present. The author reports that early observers found that almost every patient with hay fever gave a positive skin test to pollen; therefore, it was hoped that the method of investigation would be equally reliable in other allergic disorders. This hope seemed justified when between 1910 and 1930 numerous papers were published showing that in certain cases of asthma or nasal allergy, confirmation of proven sensitivities could be obtained in the same way or by the intradermal test. These techniques appeared to offer a simple and scientific method of establishing clinical sensitivity. This conception, as is well known now, proved to be a gross over-simplification which was accepted too readily and for which too much was claimed, so that the serious study of allergy for a while was thereby discredited.

Pearson rightly states that we are now in a position to assess the value of these tests in the light of information that has since accumulated. This investigator has found that there is a close correspondence between clinical allergy to pollen and the presence of positive skin reactions. However, when other inhalants (dust, feathers, dog hair, et cetera) are used, this correspondence is not quite so definite. In fact, it will be found that many patients with a history of clinical sensitization will fail to give positive reactions: if the intradermal test is employed, more reactions will be obtained than can be confirmed clinically. However, Pearson prefers the latter, except for pollen testing. Food sensitization, he has found, is less easy to assess. Apart from a small group of patients who well know that foods upset them, the clues provided by skin tests are more often than not misleading. Negative responses are often obtained in patients with proven sensitivities. Reactions are seldom obtained with fruits and vegetable extracts even when the history is definite. In some foods, such as onions, the antigen is probably contained in the essential oil which is not extracted by the usual methods. Wheat often gives more reactions than can be confirmed clinically, especially if the intradermal test is used. Infants with atopic eczema commonly give skin reactions to egg, milk, or other articles of the diet which may have been factors in the causation of their symptoms; often, however, omission of these articles from their diet fails to improve them, and these cases which respond to dietary omissions continue to give positive reactions for many years after eating these foods with impunity. He contends that in a great majority of patients with urticaria, angioneurotic edema and migraine food tests are particularly disappointing, perhaps because, contrary to popular belief, food sensitization has little to do with their causation. This clinician concludes that tests with foods seldom provide information of value, although in rare instances an unsuspected sensitization may be indicated and, more commonly, one that is recognized by the patient.

Peshkin[137] recently presented a paper in which he critically reviewed many of the pitfalls of skin tests in allergy. Because of the presence of paradoxes and of the mounting difficulties encountered with the inter-

pretation of the rôle of the tests in allergy, he has observed that there has been a great tendency in the last decade on the part of some physicians to belittle the rôle of test substances. The value of food allergens in certain allergies is particularly questioned. In fact, some persons question the need for tests at all, and far too many physicians deny or fail to appreciate that pollen asthma, with or without hay fever, frequently occurs with negative cutaneous reactions to pollen but with typical seasonal incidence. In his approach to the problem, he suggests that the first and one of the most important steps in determining causal factors of allergy is a history of the patient's ailment. The history has a direct and significant bearing on the interpretation of the skin tests and other findings. It will show that a patient can be sensitive to a given substance despite the fact that the skin and/or mucous membrane test reaction may be negative. It may also act as a guide or as a clue to the patient's tolerance. There are no short cuts to history taking. The number of tests to be used is also of importance. This is best determined by each worker according to the locale and type patient under study and usually numbers under 100. However, some allergens are of sufficient importance to warrant routine use. The use of additional tests can be determined usually from the history, diet, and environment of the patient. The selection of allergens by the majority of physicians who depend on an outside source of supply has been made more and more difficult, since many pharmaceutical houses market these allergens and each prepares them differently. This has resulted in a lack of uniformity of preparation and standardization of the test allergen, a most disturbing problem in allergy.

Peshkin advised that skin tests should be performed as single tests and not as group extracts. This method of testing is not generally approved, because if the group is positive then separate tests for the components must be made. The negative reaction may occur since a test group results in lower concentrations of each of the component substances than there would be if the constitutents were used separately. Also, this author warns that aside from the non-specific reaction obtained by the intradermal techniques of testing, another and common type of false positive reaction occurs, particularly in pollen-sensitive patients, when syringes as well as test solutions contaminated with pollen and other allergens are used. To avoid contamination of needle, syringe, and test solution, Small and others[188] have successfully devised a special chemical treatment for the needles and syringes that literally "deantigenizes" them.

From a practical point of view, there is no need for concern about the effect of drugs on the skin tests, according to Peshkin. The routine uses of epinephrine hydrochloride or ephedrine-like drugs or any of the antihistaminic drugs may cause a slight reduction in the size of a positive skin reaction and may cause a borderline positive scratch reaction (classified as plus-minus) to become negative, but in the case of pollen allergens and other potent test substances, positive skin reactions have always been demonstrated in spite of the drugs used. Likewise cortisone and corticotropin (ACTH) have no influence on the test reaction.

It is important that this investigator drew attention to the fact that serial dilution tests used by some physicians and allergists as a scientific established fact in determining local skin and systemic sensitization have not been shown to rest on fundamental and scientific evidence. Such tests serve only to add confusion and false assurance.

Food sensitization with any method of testing is discovered more satisfactorily in children than in adults. Often the offending food has to be determined by test diet when the skin tests are negative. Peshkin makes it clear that the size or intensity of a positive reaction to an allergen does not determine its importance in the etiology nor does it indicate the degree of general (systemic) sensitivity present. He contends that all forms of testing are best regarded as furnishing confirmatory rather than final evidence; to fix the responsibility requires a selected series of skin tests and other tests accurately performed and properly interpreted, together with a thorough history, physical examination, and a careful study of the case extending over varying periods of time.

ANAPHYLACTIC SHOCK OR DEATH FROM SKIN TESTS

Harris and Shure[78] reported a sudden death due to intracutaneous testing. Serum secured from the patient at the time of autopsy enabled them to prove that death was due to cottonseed extract. Cottonseed has been recognized as a potent allergen for a long time. The cottonseed extract used in testing this patient was of routine testing strength and in use in the clinic for more than ten years. The vial of extract from which the fatal dose was removed had been on the testing tray for several weeks, and samples of it had been used for testing other patients with no constitutional reactions resulting. The necessity for routine use of cottonseed extract for allergy tests has been questioned. There is sufficient evidence that cottonseed oil as commonly employed in commercial shortening, for food packing, and in salad oils, does not contain the water-soluble cottonseed protein.

It has been pointed out by expert chemists that the methods of processing edible vegetable oils renders highly unlikely their retention of any allergic activity. These facts were pointed out by Figley,[60] who reviewed the literature at that time and cited cases of his own and quoted excerpts of expert testimony before a public hearing of the Federal Security Agency, where it was established that allergic sensitivity to the water-soluble protein of cottonseed does not indicate allergy to the refined oils expressed from this seed. This author contended that many allergists have noted marked reactions following the use of cottonseed extract in skin testing, but he was aware of only two deaths prior to theirs. One was mentioned by Benson in discussing a paper presented by Bernton at the annual meeting of the American Society for the Study of Allergy in 1939. Benson stated that he had caused the death of a two-year-old child with allergic dermatitis by injecting the antigen of cottonseed meal in which a mistake had been made in the titer.[18] The other case was mentioned by McGrath while testifying as an expert witness before a hearing on cottonseed held by the Federal Security Agency.[9] McGrath testified that he had seen a six-year-old child die before the physician, administering a skin test with cottonseed, could get the needle out of the child's arm. It is probable that other deaths have occurred and have not been reported.

Wiseman and others[232] warn that the aged require the same meticulous care in testing and treatment as patients of any other group. This lesson was reported following the death of a seventy-eight-year-old woman who had marked positive reactions to food and other allergens with which she was tested. Although the usual methods of treatment were employed,

the patient expired about fifteen minutes after the skin tests were inserted.

Langley[97] reported a case of a six-year-old boy with eczema in early infancy, seasonal hay fever the past three years, who had recently developed asthma. The mother strongly suspected foods as the cause of asthma because buckwheat, spinach and egg white caused hives very promptly after ingestion. The smallest amount of carrot on contact with the oral mucous membrane would provide an immediate severe angioneurotic edema. The severity of this child's sensitivity was learned within the next hour when the nurse tested the patient with an intradermal 1:10 dilution of commercial extract. An alarming nearly fatal anaphylactic shock resulted. With the usual treatment, the patient recovered within an hour except for an intense generalized urticaria which persisted for about six hours. The mother and grandmother were unperturbed about the incident and when commended for their calm behavior replied, "We have seen him this bad many times after eating carrots."

Swineford[199] reported two cases of anaphylactic shock, one severe near fatal and the other a fatal case, from the intracutaneous test with food extract. In both instances, anaphylactic shock occurred before there was time for the skin reactions to become strongly positive.

Blanton and his co-worker[24] reported a case of death in the course of skin test in a woman who had been safely skin tested on two previous occasions. Death occurred without warning about fifteen minutes after the onset of symptoms. Neither edema or urticaria was manifest, and death was thought to be due to asphyxia from bronchial obstruction. The effect of multiple intracutaneous skin tests to food and other allergens applied to the back and the possible influence of epinephrine sensitivity and of morphine have been considered.

Peshkin[137] contended that constitutional reactions to scratch tests are extremely rare and to his knowledge have not resulted in a single fatality. When intradermal tests are used to the exclusion of all other techniques, general reactions occur in about 2 per cent of the patients, and no age group is exempt. He contends that a general reaction has not been encountered with the intradermal technique after a properly preformed scratch test in a negatively reacting patient. Fatalities have been reported, and many more have occurred and will continue to occur without the benefit of report, because there are no means of preventing a general reaction when the intradermal technique is employed exclusively, according to this author.

DIAGNOSIS

Rinkel[162] writes that while it is not necessary that every doctor be able to make a complete diagnosis of food sensitization, it is important that he be sufficiently informed on the subject that he may correctly evaluate it in the differential diagnosis. He contends that skin tests should not be discarded, neither should they be used unless they are supported by immediate and definite diagnostic programs in connection with such tests. The basis of all other diagnostic measures is the demonstration of a specific allergic reaction by deliberate ingestion of the food. In order to interpret the clinical symptoms in the diagnosis of food allergy,

it is important to have a knowledge of its nature and mechanism of reaction.

Food allergy, according to this author, may be classified as either fixed or cyclic. The fixed food allergy is one that is not affected by the frequency of the food in the diet. The first ingestion of the food is followed by definite, often violent symptoms, even if the food hasn't been used for many years. The cyclic food allergies are those that become clinically evident with the use of the food and tend to disappear with omission of the food. In other words, the presence or absence of an allergic status is determined by the incidence of the food in the diet. The course of such an allergy, according to this investigator, briefly, is as follows: If one used a food every day or so, he may be allergic to it but never suspect it as a cause of symptoms. It is common to feel better after the meal at which this food is used, than before mealtime. This is what this author called masked food allergy. He suggests that when the food is eliminated long enough that all symptoms due to its last ingestion have ceased and it is eaten again, it may—and often does—produce increased and sometimes severe symptoms which occur shortly after the meal. If the food is thereafter continuously avoided, except for tests, the following changes will occur. First, there will be an active but decreased clinical reaction, after which there develops a latent type of sensitization. In this latter state, according to this author, symptoms are not observed if the food is eaten, for example, on Tuesday, but then do occur following the use of the same food on Friday or Saturday of that same week. With further avoidance, the patient gains tolerance to the food. If, at that time, it is readmitted to the diet and used with definite regularity, these stages of sensitization will recur—first the latent and then the active state of sensitization. Should the food be used frequently, it will become a masked food allergy. Thus, one has completed a cycle of responses to the same food, these variations being mediated by either the omission or use of the food. Rinkel rightly contends that one is not allergic to food unless such allergy can be demonstrated by correctly performed food tests and such reactions must be specific and constant. Mass food allergies are a common source of error in diagnosis, he contends. They make it impossible to determine by history whether foods are either agreeable or allergic for the individual. Studies to prove food allergy require individual tests. Such tests must be supported by diet records and by instruction sheets informing patients of the source and contacts with various foods.

In a special article on food allergy, Rowe[177] set forth the reasons for delayed recognition of food allergy. Much of the material in this detailed article consists of methods of use and indications for the use of his elimination diets for the diagnosis and treatment of food allergy. For further details, the reader should consult this article which records many of the author's experiences with these diets for more than the past twenty-five years. He states that for the best results they must be used with accurate co-operation according to published directions, assuming a maximum degree of allergy to the excluded foods while possible food allergy is being studied. Proficiency with them, he contends, requires their accurate use in more than a few patients and for more than a few weeks. These diets are used as diagnostic tools, as are blood counts, tests for urinary sugar, and other tests. He feels that their accurate use not only reveals but also may exclude food allergy in the patient. He

suggests that the seasonal and geographic influences on food allergy also need recognition when dealing with the diagnosis and treatment of food allergy. The ingestion tests with individual foods are done after the initial elimination diets have produced a symptom-free patient. The approximately equal importance of inhalant allergy, either alone or in association with food allergy, and the infrequent or rare bacterial allergy and varying degrees of drug allergy have been noted.

Loveless[105] was of the opinion that the chief causes of the disagreement among allergists concerning the frequency of food allergy must relate to the diagnostic criteria employed. The individual feeding procedures of Rinkel and Randolph, as well as the elimination diets of Rowe, were introduced because the cutaneous test was found to be unreliable in this type of hypersensitivity. It is her belief that they constitute a step in the right direction, but these methods fail to take into account the influence of extraneous factors, particularly those of the psychologic origin. Consequently, she believes that an abnormally high incidence of positive results would be expected. Furthermore, there has recently been added to the diagnostic list a considerable variety of new symptoms. Although such an increase in the scope of allergy may eventually be found justifiable, this investigator is of the opinion that this can be decided only after a scientific diagnostic procedure has been devised. To attempt to set up a new method simultaneously with the introduction of new symptomatology is tantamount to testing the validity of one unknown by the use of another. There is, then, an urgent need at the moment for the creation of an adequate diagnostic technique. Loveless would like to see the introduction of controlled, objective methods to the study of food allergy.

The technique and clinical application of individual food tests in the diagnosis of food allergy was outlined in detail by Rinkel[163] several years ago. Prerequisites and the technique of individual food tests, as well as their clinical application, should be reviewed by those interested in this phase of food allergy. Briefly, the individual food test consists of complete elimination of previously regularly eaten food for periods of four days prior to a test feeding. On the fifth day, the patient reports to the office in a fasting state. After resting for thirty minutes, during which period a careful check is made of the incidence of sneezing, coughing or other allergic symptoms that occur before the test is initiated, the test food is served the patient and he is observed for another hour. If diagnostic symptoms have not developed during this time, the food is taken again at the end of an hour and the patient is observed for clinical symptoms for an additional half hour. Total leukocyte counts are performed prior to, and at twenty, forty and sixty minutes after the first feeding.

According to this author, the keystone to the diagnosis of food allergy is to have a patient symptom-free upon a known diet, for a consecutive period of a week or ten days. To obtain this state, all tests and diagnostic procedures should be coordinated. When this has been accomplished it will be possible to complete the studies without using additional individual tests. This investigator suggests the following brief outline of such a method: First is the use of skin tests, followed by the avoidance of such foods to which the patient has given reactions. If food elimination and concomitant therapy of inhalants have failed to relieve the patient in whom food allergy could be a factor, then further studies are carried out. The need for these tests will be greatly enhanced if the symptoms, observed after the patient has been under treatment, have the characteristic nature and time of reaction frequently seen with foods. When these two facts

are considered of sufficient import to warrant the use of individual testing, such tests are to be performed. If the patient has a high degree of inherent tolerance,[162] the restricted diet of foods found agreeable are to be used for a period of a week, as a test diagnostic diet. This will be possible more often than not. If the patient is found to have a low inherent tolerance,[162] it is best not to prescribe a restricted diet of a few foods but to employ a diversified rotating diet, checking possible allergies when diet and symptom records indicate these possibilities. Finally, the author warns, it is of extreme importance to differentiate first between failure to obtain relief of allergic symptoms due to our inability to make a correct diagnosis and, secondly, from our failure to obtain relief because the patient does not know where foods are contacted. He has found that one must differentiate diagnostic error from therapeutic failures due to noncooperation of the patient. The end results of the use of any diagnostic procedures in allergy, he contends, are not entirely due to the perfection with which the physician applies the method, but are as much, if not more, dependent upon the thoroughness with which a patient adheres to the findings obtained by such test procedures.

The importance of the clinical history in the diagnosis of food allergy cannot be overstressed. As pointed out by Squire,[192] the time spent in obtaining an adequate history often leads to recognition of food factors that might have been unrecognized otherwise. Frequently, an unequivocal story of childhood sensitivity to a food is given. When this is true, regardless of the results of the skin testing, it is essential to evaluate the present tolerance for that food and determine whether or not clinical symptoms will occur if it is eaten once or after repeated and long continued ingestion. Patients' histories will sometimes contain reports of food sensitivity believed to have been present, when inquiry shows that actual clinical symptoms never had occurred; instead, at some time or other, skin tests were believed to have shown positive reactions to certain foods which were excluded then and avoided subsequently without any other evidence. Furthermore, he states that food intolerance, such as that which occurs to radishes, raw cucumbers and similar foods, must be recognized as nonspecific and not be erroneously regarded as due to allergic sensitivity.

As pointed out by Randolph,[141] the specific diagnosis of food allergy in a given case challenges the powers of observation of both the doctor and the patient. It should be quite obvious, therefore, that the specific diagnosis of food allergy is a joint endeavor and, as such, should be undertaken with the patient rather than on, or even for, the patient. According to this author, then, the objectives in the diagnosis of food allergy are (1) to determine the extent to which the diet is involved by the current allergic process and (2) to determine the degree of sensitivity existing to particular foods. One must therefore employ a diagnostic approach which measures most accurately the clinical allergic reaction to individual foods.

In spite of the shortcoming of the specific food allergy history, Randolph writes that the following items are worth recording: (1) food dislikes and reasons for such, (2) suspected foods, including the evidence for such claims, (3) the evaluation of childhood dietary factors in relation to illnesses, (4) the influence on the patient's symptoms of previous dietary manipulation of any type, and (5) the quantitative food intake history. He suggests that the last is the most important and should include the number of times per days or per week that the major food allergens are eaten.

In the event that allergic symptoms are occurring in intermittent at-

tacks at an interval of once a week or, less frequently, in symptom-free periods between attacks, helpful diagnostic information may be obtained from details of the recent history and a carefully recorded food diary covering a period of several episodes. This type of patient, however, usually does not consult a physician nearly as frequently as does the individual having chronic daily symptoms. This latter group includes the patients having such constitutional symptoms as the fatigue syndrome of allergic origin (otherwise unexplained on an organic basis) existing between more classical allergic reactions.

Aside from the history, the diagnostic approach for the detection of specific food allergy in the chronic case may be considered under several headings, the aim in each instance being to prescribe an initial diagnostic diet which will avoid that individual's allergenic foods as simply and as harmlessly as possible. The method of choice and the one most accurate scientifically is to perform individual food tests with the six or eight foods the patient eats most frequently. If only one or two such tests are associated with the production or the accentuation of allergic symptoms, the patient may be assumed to have a narrow base of sensitivity: this, in turn, is usually associated with a high inherent tolerance for foods. In the event that 50 per cent or more of the first six or eight common foods tested individually are associated with the production of allergic symptoms, a highly restricted elimination diet including only test-negative foods is not indicated, for the presence of a wide base of sensitivity is usually associated with a low inherent tolerance for foods, and a sharply restricted diet, although of only a few days' duration, may do irreparable harm. The diagnosis and treatment of this type of case, the most difficult problem encountered in clinical allergy, cannot be rigidly separated. The management of this clinical situation is covered in detail in the article. The reviewers suggest that it should be consulted for further details.

For experiments with the masked ingestion tests, Loveless[106] selected eight patients on the basis of their histories for the existence or absence of allergy toward milk. These patients were given milk in masked form in conjunction with control, or placebo feedings. This approach, according to the author, gave promise of being superior to other diagnostic techniques in current use. Its chief asset, of course, was the exclusion of the psychogenic influences from the results. When the ingestion result or clear-cut history was used as the yardstick, the intracutaneous test with milk erred in the direction of giving false positive results, whereas protein fractions from milk tended to err in the opposite direction toward false negative results. Reinterpretation of the results of the ingestion test, according to the Randolph criteria, brought positive findings for three individuals who were judged by Loveless to be psychogenic or physiologic rather than allergic. The placebo feedings given two of these subjects had clarified the diagnosis. In spite of the effort to screen out such subjects through history taking, one out of eight ingestion patients was clearly neurotic, and another was presumably so "allergic" to the idea but not to the allergens of milk! This situation, she contends, is not surprising in view of the association of milk with reproductive functions and of its rôle in infant-mother relationships. At any rate, Loveless feels that the diagnostic methods which fail to take this possibility into account, whether they be ingestion tests, elimination or provocative diets, or based on food diaries, will introduce false positive findings. The risk is particularly great if one accepts as allergic such commonly neurotic complaints as headache, fatigue, chilliness, and muscular discomfort. Placebo ingestion studies

would seem indispensable. In conclusion, the need is cited by this author for re-evaluation of the symptomatology of allergy, particularly as regards the claims of Randolph, Rinkel, and Rowe, and for the development of scientific methods of diagnosis in food allergy.

Unfortunately, a survey of the literature reveals a sharp difference of opinion regarding the diagnostic procedures in food allergy according to Bernton.[20] The high percentage of false negative and false positive reactions has cast a doubt upon the value of the skin test. He has observed that cutaneous tests made with potent food extracts, carefully performed and adequately controlled, are helpful and will occasionally yield significant information. The clinical history, according to this author, is an important link in the chain of evidence in the diagnosis of food allergy as it is in the diagnosis of other diseases. Patients who are sensitive to the powerful allergenic foods, such as milk, egg, fish, shellfish, and nuts, have recognized the promptness with which reactions follow ingestion or even contact. The information acquired by skin tests may help to correlate delayed symptoms due to the skin-positive reacting foods. A diary listing the foods ingested over a period of one to three weeks and a daily record of symptoms, if any, may also serve a similar purpose. He knows that there still remains a group of patients in whom the ingestion test or so-called "therapeutic trial" is the sole means of determining food sensitiveness. The clinical history may be vague or indefinite. The cutaneous tests with food extracts may be inconclusive, as previously indicated. Under these circumstances, the ingestion test, it is agreed, offers a more accurate and specific means of diagnosis of food allergy. Bernton points out that several dietary methods have found acceptance. One of the oldest procedures was to place the patient on a starvation diet for one to three days. He was then given a diet of rice and tea. Other foods were gradually added, one at a time, and the reproduction of such symptoms as ensued were carefully noted.

Several modifications of the ingestion test have been introduced, comments Bernton. For some patients, an initial diet consisting of the negative-reacting foods is prescribed. The clinical course is observed during this trial period. Observation is continued when the diet is increased, first by test-negative and later by test-positive foods. It is upon this principle that Rowe's "elimination diets" have been based. They were first published in 1928. These are standardized diets which can be readily used in the diagnosis and treatment of food allergy. The diets may be modified according to the food history and skin reactions. They include foods which rarely or infrequently produce allergy in average patients. Rowe is of the firm conviction that "trial diet is of greater importance than skin-testing." Bernton finds that the diet, proposed by Andresen, is a very antithesis of Rowe's diet. It consists of a diet of wheat, milk, egg, beef, potato, orange, and salt—all common causes of allergy. A patient sensitive to any food in the list will promptly develop symptoms and the offender can readily be traced from this small group of foods. If there is no aggravation of symptoms within the first two days, the patient is advised to continue with it for one week. If at the end of this period there is an amelioration or disappearance of symptoms, other foods are added singly at three-day intervals, and the reactions carefully interpreted.

Randolph, in a desire to improve "current outmoded methods of specific food diagnosis," advocates the following procedure according to Bernton: (1) a period of four days during which the test food is ingested; (2) a succeeding period of four days of abstinence from the test food; (3) the

ingestion of the single test food on a fasting stomach the following morning; (4) the observation of resulting signs and symptoms. The Randolph method, according to Bernton, when applied to several foods of necessity requires an extended period for experimentation. The variation in the occurrence and intensity of symptoms, so characteristic of chronic disease, may be due to causes other than food sensitiveness. Moreover, the influence of psychic factors during such a prolonged investigation must not be overlooked. There are many allergic persons who are so sensitized to suggestion that their expression of food disagreements must be evaluated. He contends that such attitudes are betrayed when, in consultation, they exclaim: "Why the very thought of that food makes me sick."

The reliability of the ingestion test is enhanced by excluding or minimizing psychic factors. The "blindfold" technique, wherein the identity of the test food is unknown to dispenser and patient, offers that opportunity. Moreover, the suspected food ingested on a fasting stomach must reproduce allergic symptoms attributed to it. The symptoms provoked by such ingestion are determined by the affected "shock organs"—the respiratory tract, the gastrointestinal tract, or the skin. Bernton writes that in 1934 the leukopenic index, a laboratory aid in the diagnosis of food allergy, was advanced by Vaughan. The method consists of taking white blood cell counts before and after eating a normal quantity of a single food to be tested. A drop of 1,000 cells or more below the lowest fasting count is regarded as a positive index of allergy. Vaughan stressed the defects of skin-testing with food allergens and concluded that the digestion leukopenia overcame the objections. The leukopenic index as a diagnostic means had had enthusiastic supporters and severe critics. Alvarez, in a discussion of "Specific Food Sensitiveness," gave expression to an opinion which was not based on experimental evidence. The opinion, according to this author, reads: "It seems to me that we can save time and expense by testing each food by its reactions on the patient's comfort and not on his white count."

It is common knowledge that an adequate amount of allergen must be present in a given exposure for the allergic patient to develop symptoms, and that the minimal requirement varies with the individual. Loveless[107] finds that it is surprising that so little information is available concerning what might be called a "minimal provocative dose" of an allergen. Physicians have preferred to judge their subjects' susceptibilities by means of tests carried out in the skin, even though it may not participate in the clinical disorder. The reasons for this, no doubt, are the ready availability of the dermis and the difficulty of arranging for uniform, graduated exposures to such allergens as pollens. It appeared to this investigator that food allergy could be evaluated through ingestion tests carried out with graded doses of chemically standardized food extract. Although tests of the skin are of value for screening purposes, Loveless is of the opinion that the ultimate diagnostic procedure for allergic cases should be applied to the organ involved in the clinical complaint, such as the nose or the eye of the hay fever patient, the bronchial mucosa of the asthmatic, the gastrointestinal tract of the food-sensitive individual.

Tests of the skin seem especially undependable in the case of food allergy because the results so seldom parallel the clinical complaint, misleading one by false positive as well as by false negative findings. This unreliability has no doubt been responsible, according to this author, for the optimistic claims made for such procedures as the leukopenic index. Although some food allergists have recently veered away from cutaneous

techniques and are resorting to ingestion tests, they have failed to make adequate distinction between allergenic and psychogenic results. Furthermore, Loveless believes that there has been little or no attempt made to appraise the degree, or threshold, of sensitization by means of ingestion studies. In the study of cottonseed sensitivity, this author has aimed to overcome these two shortcomings of the otherwise promising ingestion test by (1) conducting all feeding experiments in a masked manner so as to control psychic factors, and (2) by using measured amounts through the feeding of standardized extracts in increasing doses at half-hour intervals until allergic symptoms develop. She states, however, that this diagnostic shortcut could be used, of course, only with those allergens which produce reliable cutaneous and/or conjunctival reactions. Cottonseed falls in this class. For less dependable foods, the ingestion test would probably have to remain the guide to sensitivity.

For several years, Lee and Squier[99] have used the simple provocative diet as an aid in the evaluation of food factors in allergic patients. This diet was first described by Andresen[14] and later modified by Black.[21] Unless the history or the observations contraindicate, these investigators used wheat, milk, egg, beef, orange and potato exclusively for trial period of approximately a week. They contend that these foods, which are the major constituents of a normal diet, provide adequate nutrition, and the regimen can be followed with a minimum of discomfort. These, also, are the foods most frequently responsible for food allergy. When sensitivity exists to any of these major foods, these investigators find that the increased symptoms are almost always evident before the end of the trial period and may become increasingly severe. When this forced and exclusive diet can be taken without the evidence of exacerbation of symptoms, both patient and physician have an adequate demonstration that the foods in question cannot be of causative importance. They state that it must again be emphasized that when exacerbations occur with this provocative diet further observation and trial are essential before the food factors can be finally incriminated. Increased exposure to pollens or other inhalant allergens may have occurred at the same time. Diet trial, regardless of the type used, is always more difficult during the pollen season in patients who are pollen-sensitive, but repeated trial in time will give a satisfactory answer. Such a provocative diet can be modified as indicated by special circumstance. It provides a satisfactory method for obtaining positive evidence of tolerance for basic foods.

These workers contend that the extreme depletion which all too often results from ill-advised and long-continued elimination diets will never occur if provocative diets are used. Often, by the time the trial diet has been completed in the allergic study, food factors can be reasonably excluded. On the other hand, when the evidence indicates that symptoms are indeed caused by foods, subsequent investigation, based on information already obtained and suggested by the history and diet record, can be carried out by the diet trial. They recognize that food allergy does occur and can be an important cause of allergic disease. Definite criteria for recognition exists, and rigid standards must be met before the diagnosis of food allergy can be accepted. Lee and Squier believe that the use of the provocative diet that they have just described will aid in avoiding unjustified elimination, based solely on subjective evidence, of certain foods. Sensitization to suggestion would be minimized. They conclude that the provocative diet is a positive aid in the identification of specific food allergens and in the intelligent management of patients with real food intolerance.

According to Walzer,[224] a study of the patient's carefully kept records of his food and drug intake and their chronologic relationship to allergic symptoms may prove to be more helpful than skin tests in the diagnosis of some allergic conditions. One may resort to stereotyped systems of food elimination and trial feedings as, for instance, the Rowe diets. However, he maintains that the more experienced investigator often prefers to vary his regime according to the patient's symptoms and needs. The gradual elimination of suspected allergens from the patient's normal diet is more likely to be successful in the long run than is the use of radical or starvation regimes. This clinician rightfully states that if these stern measures do not meet with immediate and striking success, the patient is likely to become discouraged by the severity of the regime and to seek other methods of obtaining relief.

The correct diagnosis makes the difference between an acutely ill child and a relatively well one; in fact, in two cases it was lifesaving according to Collins-Williams.[36] Although the incidence of milk allergy is low (0.3 per cent) in his series of cases, he contends that this in no way detracts from the importance of this syndrome. He points out that while his series of 3,000 patients contains many cases with relatively rare conditions such as neuroblastoma, hepatoblastoma, and adrenogenital syndrome, it contains no cases of brain tumor, diabetes, Hodgkin's disease, cretinism, diphtheria, lead poisoning, syphilis, and such diseases which are considered so important that they make up a large part of pediatric teaching in our medical schools and in hospital rounds. This investigator contends that milk allergy, therefore, is as important to the practicing pediatrician as are these diseases and should be considered in the differential diagnosis of all the conditions attributed to milk allergy which have been listed above. Otherwise, the correct diagnosis will almost certainly be missed. This author also contends that something should be said about the absence of any cases of infantile colic alone attributable to milk allergy in this series. Although several hundred cases of colic have been observed among the three thousand cases in no instance has he seen one that can be definitely proved to result from milk unless the colic was associated with other allergic symptoms. Many which were suspected to be due to milk allergy had been observed but were never proved, either because they cleared spontaneously before the criteria of diagnosis could be fulfilled or because the mothers, with preconceived idea that cow's milk is the only food fit for babies, refuse to allow their babies to be put on milk substitute. On the other hand, he has observed many infants with major allergy in whom colic was present and disappeared when their allergy was treated, often with the withdrawal of milk. Collins-Williams concludes that an incidence of 0.3 per cent of definite milk allergy is great enough that the practicing pediatrician should consider milk allergy in the differential diagnosis not only of infants and children suffering from major allergy, but also in those suffering from a wide variety of symptom complexes both gastrointestinal and otherwise.

Although a high blood eosinophilia in food allergy does occur, the physician's first thought is usually of bacterial allergy. However, Swinny[200] reports an unusual case of milk sensitivity which resulted in extreme exhaustion and easy fatigability with an eosinophil count of 97 per cent. The physical examination was normal. No parasites or ova were found in the stool, but there was 21 per cent eosinophils present. After two weeks on a milk free diet, the eosinophils dropped to 18 per cent. The next count, which was made eight and one-half years later,

during which time the patient had omitted milk from the diet, the fasting eosinophil count was 6 per cent.

Since the symptoms of allergy of the gastrointestinal tract in infants simulates so many other conditions, Nance[126] emphasized the importance of making a quick differential diagnosis or at least one that would rule out food allergy. The result of his work seemed to indicate that such a method is available in the examination of stools for the presence of eosinophils. He suggested that many years ago Haughwout[79] called attention to the presence of a large number of eosinophils in the stools of patients suffering from diarrhea. Lately he decided to look for eosinophils in the stools of infants showing other symptoms suggestive of gastrointestinal allergy, and the results were quite gratifying. In a report, he selected ten cases from over thirty patients in his practice in the past two years who have shown eosinophilia in the stools, which he considered a representative group found in any pediatric practice. The author is of the impression that the diagnosis of all the cases would have been made eventually without examining the stools for eosinophils, but in the majority a long period of trial and error was eliminated. He published the technical data necessary in preparing slides to demonstrate eosinophils in this article and concluded by stating that the examination of mucoid portion of stools for the presence of eosinophils was of value in recognizing gastrointestinal allergy in infants.

Rosenblum and Rosenblum[169] have followed very much the same line of thought in the investigation of stools for eosinophilia. Sixty infants suffering from diarrhea, vomiting, and colic, either alone or with two or three of these combinations were reported in a series as a study by these investigators. Stool eosinophils were demonstrated in all cases. They also studied a series of seventy-six infants whose stools were negative for eosinophils and these included cases of bacillary dysentery, cystic fibrosis of the pancreas, amebic dysentery, diarrhea of undetermined causes, and normal infants having normal stools. In other words, there was nothing in the clinical course of this last group to indicate any evidence of active allergy during the period of observation. The authors emphasized that the presence of gastrointestinal allergy, often due to food, may be suspected when clumps or large numbers of scattered eosinophils are found in the stools. The outstanding microscopic feature is the abundance of mucus occurring in the stools.

Tallant and his co-workers[201] endeavored to establish clearly the value of the x-ray as an aid in the diagnosis of food allergy in the small bowel. At first, a control test was made by studying the reaction of the small intestines with a barium water mixture. This test was made at least five days previous to feeding the offending allergen, and the results were considered normal. Four days later, the x-ray studies were repeated, using a test meal of barium and the suspected allergen. There was a definite motility change in the small bowel in all of the patients. One patient reported for a third study, using egg to which he was not clinically sensitive, and the motility of the small intestine was again found to be normal. Eight nonallergic persons were observed in a similar fashion, using egg, milk, pork and corn, all with negative findings. These investigators then studied five allergic patients in whom food produced allergic reactions other than intestinal disturbances. Although their allergic conditions (asthma, angioneurotic edema and neurodermatitis) were precipitated by the food tests, no changes were noted in the motility of the small bowel. It would appear from these demonstrations that the value of the x-ray in

the examination of the small bowel in the study of food allergy is definitely established and possibly answers some of the past criticisms.

That the pylorus plays an important part in the allergic symptomatology of the stomach is becoming increasingly apparent, according to Fries.[65] He suggested that any survey of several factors underlying pyloric obstruction must include hypersensitiveness to food. In this study, he selected thirty children ranging in age from four to fourteen years, who had repeatedly exhibited marked gastrointestinal disturbances within a few minutes after the ingestion of small amounts of allergenic foods. There were positive intracutaneous reactions to the offending foods in many of the children. In the control study, plain barium sulfate in water was used. On roentgenologic study made about a week later, barium sulfate in water plus the offending allergen was added without the knowledge of the patient. A predetermined amount of allergen required to produce a definite gastrointestinal disturbance varies from 2 to 12 cc (½ to 3 drams). This amount was insufficient to alter the normal roentgenogram in normal subjects.

Both series were subjected to intermittent fluoroscopy within the first thirty minutes. In the control series, the barium began to leave the stomach immediately or within ten minutes, which is considered normal. In the allergen series, it required twenty minutes or longer for the allergen-barium meal to pass from the stomach to the duodenum in twenty of the twenty-eight children studied. This investigator suggested that the roentgenograms in most part confirmed the fluoroscopic findings. He observed that one patient, who was sensitive to three different foods (eggs, fish and nuts), responded with the same gastrointestinal symptoms on different occasions. After a trial feeding with each of the offenders, involvement of the pylorus was demonstrated by x-ray in each case. This author suggested that his study seemed to support the findings of others who by gastroscopic examination of the stomach during an allergic reaction observed that the involvements seemed primarily to involve the pyloric region. He was of the impression, based on his own studies, that an allergic reaction in the region of the pylorus might account for the epigastric distress, the cramp-like nature of the pains and the rapid onset of symptoms that followed ingestion. It was his suggestion that the spontaneous relief which occurred was due to the elimination of the antigen, either by vomiting or passage to the lower bowel, and suggested a contact reaction. Fries believed that this was further substantiated by previous studies involving the rectal instillation of the antigen where he observed that contact provoked an immediate onset of symptoms which were accompanied by spasm as observed roentgenologically in the large intestine. The author concluded that the gastric retention in this report and in his previous studies may be attributable mainly to blockage of the pylorus. It was observed that the roentgenograms revealed transient abnormalities whose configurations sometimes resemble those of fixed organic lesions. This investigator emphasized that the re-exposure to the same allergens resulted in reactivation of the same shock tissues and that exposure to other antigenic foods produced the same symptoms in the same patient, and they also produced similar responses in the pylorus.

Lepore, Collins and Sherman[101] in an excellent article, endeavored to evaluate the usefulness of a small intestine x-ray examination as an objective technique in twenty patients with suspected gastrointestinal allergy due to food. The method, as described by these investigators, was according to the technique of Golden,[72] using 4 ounces of barium sulphate

in normal saline solution. The motility was observed fluoroscopically, and films were made at appropriate intervals. The especially stressed features were: (1) gastric emptying, (2) transit time of barium from the stomach to the cecum, (3) mucosal pattern, (4) tonicity (caliber of the lumen of the intestine), and (5) segmentation of lack of continuity of the barium column. Most of the patients selected for investigation gave histories suggesting food allergy with gastrointestinal disturbances. The alimentary symptoms consisted of flatulence, abdominal pain, and often diarrhea and nausea following the ingestion of specific foods. Urticaria followed the ingestion of the offending food in half of the patients, and several exhibited marked eosinophilia but, as a rule, the eosinophil count was not elevated. They explained that the commonest allergen was whole milk, which occurred in 70 per cent of the cases. These observers reported that the results of their studies showed two patients who were strongly suspected of food allergy but showed no significant change in the motor function of the small bowel. Motility changes that were observed in eighteen of the twenty, however consisted of the following: (1) hypermotility with rapid transit of barium from the stomach to the cecum in fourteen patients (hypomotility was encountered in four patients), (2) hypertonicity of the small intestine, especially in the middle and lower portions, and (3) segmentation or discontinuity of the barium column. At times, gastric emptying was delayed, but this was not a constant finding.

It was interesting to note that these observers could provoke by clinical means, by administration of the specific allergen during the x-ray study, symptoms of abdominal stress, cramps and diarrhea. Elimination of an offending allergen resulted in a significant and often dramatic clearing of symptoms. These investigators suggested that antihistaminic drugs, such as elixir of Benadryl, Pyribenzamine, Neoantergan, and Perazil, were helpful in relieving acute symptoms and also in the treatment of patients whose multiple sensitivities precluded the use of an elimination diet for any period of time. They suggested it was possible when antihistaminic medications were given, that small amounts of food allergens could be permitted in the diet. These authors are of the opinion that the rôle of food allergy in the causation or aggravation of organic disease of the intestine, stressed by many and deprecated by others, has lagged because of the lack of objective methods of study. By the use of the x-ray method of examination, using the method explained above, they consider that it has been possible to produce marked disturbances of motility in food sensitive patients, thus verifying the clinical histories of food sensitivity.

In an editorial on food allergy Lowell[108] states that there is perhaps no field of medicine in which more divergent views are held than in that of allergy to foods. One difficulty, he contends, in this field is that most manifestations ascribed to food allergy are common to many other conditions, actual or imaginary. Attitudes and beliefs regarding foods whether or not they are based on physiologic effects dependent on or independent of psychic influences, stem, in part at least, from centuries of lore—national, religious, racial, regional and medical. This author points out that manifestations claimed by some to be of allergic origin are not only numerous but extremely diverse, so much so that there is hardly an ache or a twinge that may not fall within the purview of the allergist. The nature of these reactions, therefore, may give no clue as to the rôle played by allergy. Indirect tests can be regarded as valid only after they have been shown to be so in instances of proved allergy to foods. This

remains to be done. Therefore, the use of procedures such as the leukopenic index, changes in the number of circulating eosinophils, or skin tests, cannot give us the information we need.

Although it is clearly not sufficient to say that an allergic mechanism operates because a certain reaction follows the ingestion of one or more foods, the demonstration of a cause and effect relationship is nevertheless essential. This investigator suggested that the food should be completely disguised by some means or other, and perhaps it is best given in capsules or by stomach tube. Other foods given in the same manner should fail to cause any reaction. Furthermore, the reaction should be consistently reproducible as regards type and time of its occurrence. Once these criteria have been met, a cause and effect relationship would appear to have been established, and it would seem reasonable to ascribe the reaction to an allergic mechanism. Such a conclusion, Lowell admits, is not strictly logical, however, because a cause and effect relationship is not solely peculiar to allergic mechanisms, however much we as allergists may see fit to regard it so. Nevertheless, he contends, that much can be done on this problem. A close study of the relatively small number of carefully selected patients having indubitable allergy to foods, as judged by the type of allergy to foods, would go far toward clarifying the subject and giving us a useful understanding of allergic reactions to foods.

Lowell suggested that such a study might include, in addition to those studies mentioned, quantitative tests for skin sensitivity and skin-sensitizing antibody, determination of the dosage required to produce a reaction, the interval required before the reaction takes place, the duration of the reaction, and something might also be learned concerning the behavior of the white cells, the eosinophils, and the value of x-ray studies. He concluded that all this is tantamount to saying that we must learn far more about what appears to be familiar before we can effectively tackle the problems that face us in food allergy.

THE PSYCHE

Burden's[29] recent article, "The Role of the Psyche in Allergic Disease," is an excellent one and should be of special interest to all those who practice allergy. He remarks that Weiss and English[226] in their textbook, Psychosomatic Medicine, state: "Allergy and psychosomatic medicine have much in common. The allergic population and the neurotic population are so numerous that they must overlap. Therefore, if for no other reason, these disorders exist together in many people." This author contends that in private practice and in clinics, he finds these statements to be true and, therefore, he is called upon to treat neurotic allergic patients and allergic neurotic patients. In many cases, there is clear evidence of more than just "overlapping." There is evidence of direct influence of psychogenic factors on the allergic state itself. The average allergist, he contends, has been reluctant to delve deeper into the actual rôle that the psyche may play, although he has accepted what has been known since the ancient days; that emotional disturbances affect or even precipitate attacks of asthma or hay fever. It is this author's contention that as the allergist develops the immunology of allergy, the rôle of the psyche is forced into the background. A good many allergists still hold the opinion that where a patient gives evidence of definite positive skin reactions which coincide with his clinical manifestations, that the patient is definitely allergic and the psyche can play no part in his symptoms. To point out further the reluctance on the part of some allergists to look into the

psyche, Abramson[3] stated that up to the period 1936-1946 the *Journal of Psychosomatic Medicine* had twenty papers relating to the emotional problem in the allergic state, whereas, in the *Journal of Allergy*, in the same period, only one brief report appeared on the same topic.

Notwithstanding the above prejudices, this author feels that in recent years there has been a steadily increasing interest on the part of allergists in the rôle of the psyche in allergic disease. Also, psychiatrists are beginning to accept the fact that there is such a thing as allergy, from the immunologic standpoint, which can be affected by—rather than entirely produced by—psychogenic factors. Numerous articles are now appearing on the psychodynamics of allergic disease, and psychiatrists such as Wilson[229] have agreed that, although psychosexual maladjustments may make a nose more sensitive to pollens, an external agent such as pollen may produce an attack, and that local sensitivity alone, in the absence of psychologic stimulation, may be sufficient to produce an attack. Here at last, this author comments, we see evidence of a new approach to the patient with allergic disease. This approach, if practiced by the allergist, will yield better results than he has had heretofore in the treatment of many of his patients. Burden added a word of caution when he suggested that although allergists and internists are urged to accept the fact that the psyche does play a rôle in allergic disease, he would also urge that the greatest of care be exercised in the evaluation of physical and psychologic factors in every case. He contended that it is just as wrong to have a closed mind to the importance of true allergic factors as it is to have a closed mind to the importance of psychogenic factors. In other words, as physicians "we must combine the functions of internists, allergists and psychiatrists" as was suggested by Brown, and by doing this, we recognize the causative factors in both fields. Where psychogenic factors either predominate or are the sole cause of the patient's illness, this observer contends that the physician must determine whether he is willing and sufficiently confident to treat the patient, or whether he should refer him to a psychiatrist. Above all, the alert allergist should be able to distinguish the true allergic patient from the so-called para-allergic patient. Such an approach will result in much greater relief of symptoms for a great many people with allergic disorders.

Kaufman[91] reviews his clinical experience with 600 patients and analyzes some of the reasons why patients who are allergic to specific foods, as proved by clinical testing, deliberately eat such foods, thus creating self-inflicted, food-induced allergic illnesses. He states that an individual's pattern of choosing and eating foods becomes psychologically highly structured, conditional reactions. Foods have emotional values for an individual over and above the hunger-satisfying capacity of all foods. Some foods are "gustatory pleasure" foods, "pleasurable association" foods, "security" foods, "reward" foods, "fetish" foods, et cetera. The patient's urgent need for ingesting foods in the above categories in times of stress may be so great that the emotional support derived from eating them far outweighs the consequences of self-inflicted, food-induced allergic illness. Sometimes a patient genuinely forgets that he is not supposed to eat the allergenic food; sometimes, after a period of abstinence from the food he is merely curious to see if eating the food will make him sick. Sometimes suggestions of his family, friends, or other physicians outweigh the recommendations of the allergist. Also, a patient who has severe guilt feelings or is depressed, or wants special attention or special privileges from others, may experience strong drives to eat allergenic foods until he is

quite sick. A tentative explanation is offered from the increased severity of self-inflicted, food-induced allergic reactions in individuals who are experiencing an acute episode of repressed anger or resentment at the time of ingestion of the allergenic food. This explanation is given in terms of what is known about the physiology of this type of psychosomatic reaction and in terms of the cellular antigen-antibody reaction. Undoubtedly, the situation is more complex than indicated by this initial formulation.

The allergist, by understanding that changing eating habits constitutes a severe dislocation in the patient's ordinary way of living, can help the patient by rendering supportive and reconstructive psychotherapy, and in this way can help the patient to make a better adjustment to the stresses of his life and to the necessities of allergic treatment. The physician must see his patient at sufficiently frequent intervals to give him the approval he desires and to reiterate therapeutic suggestions about allergic management. The author also states that the allergist should suggest definite time of retesting the patient's tolerance for allergenic foods: since this reduces the patient's curiosity to try eating the food whenever he chooses. If the patient admits to having eaten an offending food, the allergist should be kindly but at the same time insistent that the patient follow the therapeutic program.

It is frequently noted in allergy practice that patients with well-marked skin reactions are inconsistent in their clinical response.[33] The reasons for this are not clear. Miller and Baruch[118] studied a patient in whom the inconsistency was particularly striking, and they presented their observations and offered a possible explanation. The patient was a boy, three years and eight months of age, with a history of asthma for one year previous to this visit. Between attacks of asthma, there was nasal obstruction. Since infancy he had shown a mild aversion to eggs. He was a timid child whose chest was typically asthmatic. Skin tests resulted in 3-plus to 4-plus positive reactions to practically all the pollens, many positive reactions to other inhalant substances and to numerous foods, that to egg white being most marked. At no time was restriction placed on diet or physical environment, and no specific allergy treatment was administered. A study of the pollen counts, the weather, the diet, and the immediate physical environment showed no correlation between the asthmatic attack and exposure to reacting allergens. These authors believed, therefore, the thesis as held by Walzer[33] and Hill,[82] that the positive skin reactions merely represented an immunologic response to previous exposures to the allergens. Play psychotherapy with the child and psychoanalytically oriented psychotherapy with each parent were instituted. As a result, the data from these sources indicated that the emotional interplay could be correlated with the asthmatic attacks of the child. These workers presented evidence that indicated that the emotional pattern consisted of a feeling on the part of the child that he was not loved and that when his anger at his parents on this account was blocked from expression by his fear, asthma would result. In contrast, when his anger was expressed and he was made to feel secure in his expression of it, his asthma could be aborted or, when present, cleared. Miller and Baruch concluded that, in this patient, emotional problems were expressed somatically as clinical allergy which functioned within a pattern set by his allergic constitution quite independently of his exposure of reacting allergens.

Kaufman[92] continued with the psychosomatic aspects of food allergy and contended that certain patients experience untoward idiosyncratic re-

actions when they eat certain wholesome foods. Illness due to such reactions may be either on a psychogenic or allergenic basis or both. The relative importance of psychogenic and allergenic factors in the production and continuance of food-induced illness must be estimated correctly in order to plan a correct program of therapy. This clinician states that foods become endowed with various dynamic emotional meanings according to the person's upbringing, cultural and religious training, and personal life experiences. Psychogenic food reactions may include anger, anxiety, anorexia, depression, euphoria, feelings of security, guilt, hostility, passive-dependent attitudes, pleasure, syncope, and relaxation. He suggests that the most common untoward idiosyncratic psychosomatic reactions to food include nausea, vomiting, epigastric discomfort or pain, intestinal cramps, aerophagia, belching, and rarely diarrhea—all being part of the riddance reaction. The food-induced allergic, mental, fatigue, and pain syndromes are described. These may occur singly or in any combination, and may be associated with any other allergic syndromes. The patient's response to combined allergic and psychological therapy is illustrated by case reports.

He believed that many patients are relieved of allergic ill health when they abstain from known offending foods. However, some of these patients will have conscious or unconscious needs at certain times to eat allergenic foods which they know will make them sick. The subtle nature of food-induced self injury readily escapes the attention of the patient's family and friends—and even, sometimes, of his unsuspecting physician. Self-inflicted, food-induced allergic illness can become a recurrent problem until the physician can understand the basic psychodynamics of such self-injurious behavior, and can then help the patient to make better adjustments to life problems. He concluded that the best management of all patients with food allergies requires both expert allergic therapy and expert psychotherapy.

Goin[71] was of the opinion that the effects of the various emotions on the intestinal tract was extraordinarily well known. He was surprised to learn that in spite of this widespread and common knowledge we, as physicians, give such little thought to the emotions and emotional conflicts as a possible factor in producing a great deal of the abnormal gastrointestinal behavior. Vomiting due to pyloric obstruction and pain and vomiting from intestinal obstruction usually offer no great problem of diagnosis to the roentgenologist. In general he claimed, it is their part to establish, or to eliminate the possibility of organic disease. Nevertheless, he admitted there were times when it was possible to suspect emotional disturbances or an unconscious conflict if it is kept in mind that these reactions are not infrequent and that they lead to disturbance of the gastrointestinal tract. Following these remarks, he presented a case of profound emotional conflict which was actually diagnosed from x-rays of the gastrointestinal tract. A white woman, fifty-four years old,—and it is essential to her history to state that she was of Jewish extraction—complained of vomiting, abdominal pain and diarrhea for twenty-two years. During that time she had undergone fifteen operations with no relief from her symptoms. The patient did not appear acutely ill, had lost no weight, and, except for heavy scarring of the abdominal wall, the physical examination was negative. Shortly after admission to the hospital, an allergen-free opaque medium of barium sulfate in normal saline solution revealed a normal pattern and behavior of the intestinal tract. During the examination, the patient talked freely with the examiner and told him that she

was allergic to pork—but no one would listen to her or believe it. With this in mind, the possibility occurred to Goin that this educated and cultured individual who believed herself agnostic, was suffering from an unconscious conflict; that when she ate pork it resulted in an emotional storm which passed over the sympathetic chain and produced a marked and dramatic effect in the gastrointestinal tract. The patient was informed that it would be necessary to repeat the gastrointestinal study. Finely ground pork was mixed with the barium, normal saline solution, and she was unaware of any difference between this mixture and the one used during the first examination. The roentgenologic examination was negative; identical to the first one that was made on admission. The fact that she had taken a great deal of pork with no changes in the behavior of the gastrointestinal tract was thought to eliminate pork as an allergen. She was very cooperative and willing to submit to the third examination. The same opaque medium was used as in the other examinations and soon after it had been taken she ate a small piece of well-cooked pork. Within thirty minutes, she experienced violent abdominal pain, and an x-ray film of the abdomen showed a striking change in the small intestine.

Goin suggested that this was an objective demonstration of a psychic lesion—an emotional storm resulting from an unrecognized conflict in the unconscious. In conclusion, this author made it plain that the roentgenologists have become increasingly conscious of the small intestine and its diseases. As a matter of routine, they recognized cicatrizing enteritis, ileocecal tuberculosis, tumors and manifestations of dietary deficiency. But in this instance, he explained, the purpose of his paper was to direct attention to other causes for alterations in the behavior of the intestinal tract and that these causes may be as far apart as the psychological states and specific allergies.

In a very interesting paper on changes in tissue sensitivity associated with varying life situations and emotions; their relevance to allergy, Graham, Wolf and Wolff[75] presented evidence on the following three points: (1) that man reacts adaptively or protectively in similar ways to a variety of noxious stimuli; (2) that he may react to threats or symbols of assault as though they were assaults; and (3) that consequently it may be difficult to ascertain what aspects of a total situation are really relevant to the observed reactions of the individual. In particular, these investigators suggest that ingested chemical agents and foods may sometimes take on special significance not dependent on their chemical or physical structure.

The study of cutaneous vascular reactions in patients with urticaria, reported in detail elsewhere,[76] is cited by these authors as illustrative. Thirty subjects, seventeen women and thirteen men, who had had repeated attacks of hives or whose present attack had lasted for three weeks or longer, were studied. In each case, a relatively complete life history was obtained, with particular reference to an understanding of the setting in which the first and subsequent attacks occurred. An important part of such understanding was a knowledge of the patient's feelings about the situation and his general behavior with respect to it. Note was made of foods ingested and of exposure to other substances which might conceivably have acted as allergens. It was found that there was an almost invariable relationship between an attitude of a particular kind and attacks of urticaria. The patients considered themselves wronged or injured and felt that they could do nothing to improve the situation. No

correlation between exposure to allergens and attacks of the disease was discovered.

Food Sensitivity.—These investigators state that it is conceivable that foods, by virtue of particular chemical or physical structure, sometimes give rise to antigen-antibody reactions and subsequent clinical manifestations of food sensitivity. However, they contend, that the evidence for and against the occurrence of such reactions and their importance in clinical medicine is difficult to evaluate. In any event, before it may be inferred that such reactions do exist and are clinically important, patients suspected of food sensitivities must be tested so as to preclude conditioning factors, since all the reactions may be exhibited in response to stimuli which have a threatening or other significance to the particular individual concerned. For example, it has been maintained that migraine headache is frequently a manifestation of food "allergy." The difficulties involved in reaching such a conclusion are illustrated by the following experiment as cited by Wolff.[233]

Four able physicians, experienced in experimental methods, and themselves migraine patients, were the subjects. These four physicians, who were of the opinion that they could predictably produce migraine headache in themselves by eating chocolate in any form and in minimal amounts, were each given a set of lettered, sealed envelopes, with the key to the contents held in the laboratory and unknown to the subject. Each envelope contained either 8 gm powdered chocolate or 8 gm lactose in eight black capsules. The two sets of capsules were indistinguishable in appearance. Two subjects ingested the contents of an envelope at convenient intervals. One subject ingested the contents at regular intervals, three times a week. The fourth subject, who commonly awoke on Saturday morning with a migraine headache attack after eating chocolate on Friday evening, ingested his capsules on Friday evenings for a period of four months. All were instructed to include no chocolate in their regular diet. Careful records were kept by each subject, including the following data: the letter on the envelope, the date and time of ingestion of the contents, the date and time of onset of all headaches experienced during the experimental period. It was found in these subjects that headaches sometimes followed the chocolate, sometimes the lactose, but most commonly attacks occurred without reference to the ingestion of capsules. Migraine headaches followed the ingestion of lactose just as frequently as they followed the ingestion of chocolate. According to these investigators the data thus accumulated indicates that, in these individuals who considered themselves "allergic" to chocolate, even in minimal amounts, the occurrence of their headaches was no more related to the ingestion of chocolate than it was to the ingestion of lactose. According to Graham, Wolf and Wolff, no well-controlled clinical study has yet been reported to support the contention that migraine headache is an allergic reaction, or to prove that the benefit from prescribed diets is specifically due to elimination of offending allergens. These workers pointed out that the mucous membranes of the nasal and paranasal structures exhibit vasomotor changes as a part of the reaction to allergens and may give rise to headache. But in the case of the headache which accompanies the nose reaction, as well as in the case of the migraine headaches, the assumption that the allergens are responsible for the symptom must be closely questioned in any given case until proved valid.

Graham and his co-workers also list three interesting case reports and

suggest that the observations made in these instances further emphasize the necessity for caution in diagnosis of etiologic factors. The observations they reported were made on patients in whom food sensitivity seemed relevant to their major complaints. The patients were able to relate closely their symptoms to the ingestion of even minimal amounts of the supposedly noxious substance. A simple experiment demonstrated how unpredictable the relationship was, the reaction being apparently more dependent on seeing, tasting, smelling, and hearing of the agent than upon its chemical and physical nature. As an example, only their Case 3 will be reported here. A study was made of a thirty-nine-year-old woman who for about three months complained of wheezing, running eyes and nose, and hives soon after the ingestion of milk. Skin tests were positive to milk and fish. A stomach balloon was inserted and, after a control period during which motility of the stomach was observed, 50 cc of milk was introduced. The patient was told that the introduced liquid was water. She was then told that a specimen of gastric secretion was to be taken, but actually nothing was withdrawn. Her nasal mucous membrane was examined before and after the administration of milk, and it was found that there was less secretion and congestion after the milk than before. She had no sneezing.

These investigators have demonstrated that foods ingested under one set of conditions are followed by violent reactions which are absent when the same substances are ingested under other conditions. Therefore, they contend, that in assaying the tissue sensitivity of an individual to certain assaults, including ingestion of foods, it becomes necessary to appraise their effects in terms of the setting and feeling states under which they are administered. Without such appraisal, the nature of the sensitivity reaction cannot be accurately defined. They contend that it is obvious that the summation of the effects of various factors is often important, and for optimal therapeutic effectiveness those which are most important must be defined and dealt with.

MANAGEMENT

According to Bernton,[20] treatment is instituted after the identity of the allergenic foods has been established. It consists primarily of the elimination of the food or foods presumably responsible for symptoms. An adequate diet must be prescribed to prevent loss of body weight, and the addition of vitamins is essential. In the case of infants, whose normal diets are naturally restricted, modifications or substitutes become a matter of urgency, he warns. This investigator knows from experience that the physician is inevitably confronted with an enigma when the patient asks the question: "How long must I give up the food?" The period of abstinence may extend over many years or until some loss of sensitization occurs after a short period of avoidance, provided the tissue cells are not stimulated by repeated exposure to the allergen.

Some authors, Bernton states, have advocated oral or parenteral desensitization with some foods, as egg, milk and wheat. Desensitization by means of the hypodermic injection of food extracts follows the same principles as are applied to desensitization with pollen extracts. Supportive treatment by the administration of dilute hydrochloride acid and pepsin or the use of pancreatin with trypsin should be borne in mind for patients who exhibit subacute or chronic gastrointestinal disturbances. The European school has recommended the oral use of peptones, derived from various animal and plant foods. They are administered in small amounts

one hour prior to each meal and are designed to create a state of anti-anaphylaxis. Urbach's propeptans represent an elaboration of this method. The conclusion, however, has been reached by many of our observers that the results of desensitization therapy in food allergy as a rule are not effective and do not justify the expenditure of time and effort. Complete avoidance of the allergenic food for an experimental period of time is the treatment of choice. Bernton also draws attention to the fact that in the case of the allergic patient, there are factors pertaining to his diet other than the elimination of the allergenic food which command attention. That is notably true of asthmatic victims. Patients should be warned not to eat so-called "hearty" or heavy meals. Moreover, they should be discouraged from eating solid foods immediately before retiring. "Too full for words" denotes interference with the normal movements of the diaphragm as the result of a distended stomach, and an encroachment upon pulmonary ventilation. To the chronic asthmatic with distended lung alveoli, contracted bronchioles and a tenacious secretion within them, such encroachment adds to his distress. Small and frequent meals will relieve the condition.

In a series of studies in which the influence of allergen contact was investigated, Tuft and Heck[211] have made some very interesting and important observations. They verified the clinical impressions that allergenic contact is extremely important in the induction of sensitization; more so in atopic persons than in normal persons. Thus, sensitization more frequently follows exposure to food allergens which are eaten frequently and in larger amounts than exposure to those eaten only occasionally and in small amounts. This was substantiated since these investigators found that there was a higher incidence of positive skin test reactions to food frequently eaten (tomatoes, chocolate, or peas) than to those which are infrequently eaten (goose, chestnut, green pepper, and the like). The factor of allergenic contact in these instances probably is not the sole one. Undoubtedly, the amount of active allergen present in a particular food also must be important but, as shown by these workers it required a combination of two factors, namely a potent sensitizing active principle as well as extensive allergenic contact, perhaps aided by hereditary predisposition to bring about definite sensitization. Sensitization, once induced, may persist for extremely long periods of time as exemplified by sensitization to horse serum. Since we have demonstrated that a positive skin test reaction to horse serum constitutes definite and incontrovertible evidence of previous contact with horse serum, it should apply equally to other allergens, inhalant or food and thus explain the existence of many positive reactions which appear to have little clinical significance (nonclinical positives). Just what it is that converts a nonclinical positive into a clinical one, associated with clinical symptoms, still remains to be determined. Unusual or excessive antigenic stimulation undoubtedly is a factor. These investigators warn that allergic patients, especially children, with positive tests to commonly eaten foods should be advised against eating these in large amounts, since excessive antigen contact may convert a nonclinical sensitization into a clinical one.

The therapeutic aspects of the food allergy problem may be considered to best advantage under two headings, according to Randolph.[141] The first includes cases with a narrow base of sensitivity (high inherent tolerance for foods). The cardinal principle in the management of cases of food allergy of this type is the complete and prolonged elimination of the incriminated foods. Immediately after the complete avoid-

ance of a masked food allergen—that is, for several days to several weeks—the ingestion of a relatively small amount of a highly allergenic food may result in an acute, and sometimes violent, symptom response which is described by Rinkel[162] as the phase of hyperacute sensitization. In the majority of cases of cyclic food allergy, the phase of hyperacute reaction will persist only a few weeks if the patient avoids or eliminates the particular food completely. In the majority of instances there ensues, with the passage of time, a progressive decrease in the degree of specific sensitization which eventually permits the reintroduction to the diet of the previously eliminated food.

This author now suggests that the question arises as to how and when one should reintroduce a food to the diet. From the therapeutic standpoint, he contends that the object in returning a previously eliminated food to the diet is to avoid the production of allergic symptoms, which of course is quite in contrast with the objective of producing allergic symptoms for the purpose of diagnosing specific sensitivity. Although it is admitted that something is known about how such a food should be returned, there is no concise rule for guidance as to when it is safe to try it. Randolph condends that the interval of usage of a food that can be tolerated without symptoms must be worked out gradually. It seems desirable to start by eating an average serving once in seven days. If this schedule is tolerated at the end of a month, the interval may be reduced to once in five days, and perhaps later to once in three days. Under no circumstances, he advises, should the patient return the food indiscriminately, for this is almost certain to result in resensitization.

This investigator states that there are numerous factors which have a bearing on the question of when a food may be returned to the diet therapeutically; these include the initial degree of sensitivity as judged by the speed of onset and severity of symptoms in association with the individual food test, the duration of avoidance, the complexity of the food problem and the presence of concomitant inhalant sensitivity or other physical factors existing at various seasons. Although generalizations in this direction, he contends, are hazardous in view of these variables, yet an initial attempt to return a food may usually be made between three months and a year after complete elimination was started. There might be an increase in the degree of sensitivity following the partial avoidance of a food allergen. For example, the incomplete elimination of milk, by permitting the use of butter and milk in cooking, not only keeps sensitization active but at least in certain cases may enhance it. Randolph agrees with Rowe[174] and Rinkel[162] that one cannot be expected to develop tolerance for a food by the use of it in infinitely small amounts on a progressive schedule. Rinkel believes that any improvement that seems to follow such a plan is likely to be explained on the basis of the masking of symptoms. There are certain patients who fail to develop any tolerance as the result of the prolonged avoidance of a specific food in which Rinkel describes as a fixed food allergy in contrast to cyclic food allergy as described above.

The second group of patients to be considered in the treatment of food allergy are those with a wide base of sensitivity (low inherent tolerance for foods). If the patient has a low inherent tolerance for foods, diagnostic procedures for the detection of food sensitivity may have to be continued from time to time throughout a predominately therapeutic phase of management, in view of the fact that this type of patient should not be placed on a highly restricted diagnostic diet

because of the tendency for sensitivity to spread. Although, as this author states, there has been no entirely satisfactory therapeutic approach to this problem, the most workable program appears to be the use of all tolerated foods on a rotating schedule, as suggested by Rinkel.[164] Randolph emphasizes that the classification of cases of food allergy as to the extent of involvement of the diet is a matter of relative degree. This concept is enlarged and described in detail in the article. However, it is important to realize that the author notes that individual patients vary from those sensitive to a single food to those approaching the ultimate of being complete allergics. As the therapeutic approach in one extreme is quite different from that recommended in the other extreme, intermediate cases are handled to the best advantage by avoiding the foods to which the individual is most highly sensitive, by the use of botanically related foods, and those judged to be cumulative offenders in spaced feeding with a sufficient interval between doses to avoid the production of post-ingestive symptoms. In conclusion, this author suggests that a highly restricted diagnostic diet may be employed with relative safety if the patient has a narrow base of sensitivity; it is contraindicated if the base of sensitivity is wide, for such a patient has a tendency to acquire sensitivity readily to any food used in oft-repeated feedings. The treatment in either instance consists of using tolerated foods on a rotating diversified schedule, completely eliminating incriminated foods and using those botanically related on a schedule least apt to be associated with a spread of sensitivity thereto. The complete elimination of a food is usually associated with a gradually diminishing degree of sensitization which eventually permits its reintroduction into the diet. The exception to this rule, of course, as the author pointed out, is fixed food allergy in which the degree of sensitization is not diminished by prolonged elimination.

Because sensitivity to the protein fraction of cottonseed is often of high degree, allergists have advised avoidance of dust from mattresses and furniture stuffed with cotton linters, food containing cottonseed flour, and cottonseed oils used in salad dressing, vegetable shortening and oleomargarine. Mitchell[120] contends theoretically that there is no reason to anticipate that sensitivity to the water-soluble cottonseed protein would indicate associated sensitivity to the oil. However, it has been assumed that the refined oil might contain traces of protein sufficient to produce symptoms.

In order to investigate this point, Mitchell selected eleven asthmatic patients, who were clinically and immunologically highly sensitive to cottonseed protein and all of whom had experienced symptoms either by ingestion, inhalation or injection of this substance. According to the history, the ingestion of certain brands of fig newtons, cookies, cup cakes, graham crackers, health breads, "cake" doughnuts, and candy bars were followed within a few minutes by one or more allergic symptoms of the skin, gastrointestinal and respiratory tract. "Raised" doughnuts and edible cottonseed oils could be eaten with impunity. For example, it was found that when the patients were exposed to edible cottonseed oils by skin tests, mucous membrane tests, inhalation, ingestion, and intramuscular injection, no local or constitutional reactions occurred. In the management of food allergy, this investigator concluded that in view of these findings it seemed unnecessary to advise patients sensitive to cottonseed protein to avoid foods containing cottonseed oil.

For a detailed discussion of the diagnosis of specific food allergy and its management, the reader is referred to a monograph by Rinkel, Randolph and Zeller.[165] They state that the diagnosis and treatment of food allergy are not separate procedures; the diagnosis is almost the entire treatment for the co-operative patient with a high degree of inherent tolerance. In continuing, we shall quote them verbatim:

"*Immediate Specific Therapy* (high inherent tolerance for foods): The cardinal principle in the treatment of patients with a narrow base of sensitivity resulting from a high inherent tolerance for foods is the complete avoidance of the incriminated foods. There is no other really satisfactory treatment. The elimination must be complete and continuous: no amount of the specific food may be considered so small as to be disregarded. The patient must be instructed to follow the therapeutic program without change for a specified period of time. Experimental variations therefrom are to be made by the physician in view of the patient's symptom record on such a diet. Under no circumstances should the patient assume the responsibility of making dietary changes in his specific instructions. Any prescribed diet will be given in terms of the immediate conditions. If either concomitant or thermal factors change, additional instructions and manipulation may be necessary. The cardinal principles in the treatment of patients with a large number of sensitizations which is the result of their low inherent tolerance, are identical in respect to elimination as those given for the patients with a high inherent tolerance. In addition, there is the necessity to forestall the development of new sensitizations which will occur with greater frequency, if strict substitution is the choice of treatment. These patients invariably need diversification and rotation of their foods. Diagnostic procedures cannot be completed immediately because this grade of allergy absolutely precludes the use of highly restricted diets. Thus diagnostic studies often must be continued intermittently throughout the entire phase of management or until relief is established. To illustrate our method of treatment for this type of patient, the following case record is given in detail. A patient tested on twelve common articles in the diet, was found to have postingestive increases in symptoms from nine. This finding indicates that we are dealing with a patient who would be expected to sensitize easily. Therefore, the diet was not restricted to the test agreeable foods. It was enlarged, rotated and specific foods were tested as our observations and the patient's symptoms incriminated them.

"Individual cases vary from those sensitive to a single food to those approaching the ultimate of being allergic to all foods. The therapeutic approach in one extreme as outlined above under high inherent tolerance is entirely different from that of the patient with many allergies. Intermediate and severe cases are handled most advantageously by avoiding completely all foods which produce symptoms under test conditions and rotating and increasing the number of foods used, so as to avoid an increase in incidence of the permitted foods. Rinkel has emphasized the relation of wheat and corn sensitivity by the rule, 'When a physician has found a patient sensitive to wheat, his first and immediate duty to that patient is to determine the specific effect of corn.'

"*Delayed Specific Therapy:* There are two distinct and often widely separated components of specific therapy for food-sensitive patients. The first is to determine and eliminate the offenders. The second is to ascertain when sensitization is lost, that is, when the patient has gained tolerance to these foods. Then the patient must be taught how to use this food or invariably he will become sensitive to it again. There are few, if any, exceptions to this return of allergy. Then, too, every patient must be taught how to live with his disease.

"If the patient has a high inherent tolerance, avoidance is continued for three months. Then a test is made, identical to the original food test, to determine if compatability exists for this food. If it is not agreeable, it is omitted another three months and tested again. If the patient is still sensitive, another test is made three months later. This procedure of omission and testing is carried out until the patient has either gained tolerance or a period of twenty-four months has elapsed. If tolerance is not gained by this amount of avoidance, the food may be considered as a fixed allergy and dropped from the diet.

"At whatever interval tolerance is established as determined by testing, the second feature of this program is placed into effect. When tolerance has been achieved to a previously allergenic food, it is admitted to the diet and used once

daily in normal amounts at intervals of once every five days for six feedings. If it is still compatible, it is then increased in the diet once daily every third day for the next three months. The majority of food allergies will recur if the food is used more than once daily, but these are exceptional instances, and it is not desirable to try this with an important food. The danger of recurring sensitization is too great.

"Eventually, all food to which the patient had been found sensitive in the early period of study will be evaluated and used in the proper manner. When this is done, the patient is allowed to discontinue direct observations but is advised to continue rotations and diversifications as were needed to accomplish freedom from symptoms."

Substitutes for cow's milk in infant feeding has always been a problem. Glaser[70] reports that the use of cow's milk is of itself a substitute feeding. However, it has been used so long for this purpose that it is regarded by the laity and by most physicians not as a substitute but as a "natural" food for human infants. Years ago he pointed out that the only "natural" food for the human infant is human breast milk, and that the cow, after thousands of years of domestication, still produces milk primarily designed for calves and not for human beings. This being the case, Glaser states that any substitute for cow's milk, provided it meets the requirements of the infant satisfactorily, is just as "natural" a food as cow's milk, a concept which is difficult of acceptance both by laymen and by physicians.

Following the report of Osborne and Mendel[131] that soybean contains all the amino acids necessary for the normal growth and development of the human infant, Tso,[205] a Chinese physician, sought in the soybean a substitute for breast milk and for cow's milk, the latter apparently an expensive item in China. After he succeeded in raising one infant from birth to about the age of six months on a substitute milk made from soybean without the addition of any protein of animal origin Glaser used soybean milk in potentially allergic infants directed at the prophylaxis of allergy to cow's milk. Sixty-five infants were fed soybean milk from the time of birth as the sole milk substitute for varying periods.[69] All but nine of these infants (about 13 per cent) did well on the soybean milk, and Glaser and his co-workers were thus able to confirm and extend the observations of Tso in his single case.

Soybean milk did not attain any great popularity until Hill and Stuart[85] introduced a practical preparation in 1929, which soon became commercially available. Since then a number of other similar and satisfactory products have appeared on the market. However, with the introduction of the soybean on a large scale into various industries in this country for use in the manufacture of paint and plastics and many other articles, and also its introduction as a food, particularly as a protein extender in various kinds of meat preparation, and bread, it was only to be expected that infants would eventually not only be found sensitive to cow's milk but also to soybean milk. Under such circumstances this author states that human breast milk would appear to be an ideal food. However, it is not always available and when available is quite expensive. If the milk is produced for allergic infants, the mother should be on a special diet, omitting egg, for example. These factors render it impractical for general use. Since the casein of goat's milk is closely related to that of cow's milk, it is only rarely that goat's milk, for reasons not now well understood will prove satisfactory in allergy to cow's milk when, as is commonly the case, the allergy is due to the casein fraction which is heat stable. In the case of allergy to lactalbumin, which is large-

ly, but not completely, species specific, goat's milk will occasionally be a satisfactory substitute for cow's milk, but not commonly for evaporated or other heated forms of cow's milk because heat denatures lactalbumin. The milk of the mare and of the ass are more like human milk than that of any other animal used for food. Qualitatively, it resembles human milk in that more than half of the protein is readily digestible lactalbumin. The mineral content is about the same as human milk. The digestibility of both, as judged by *in vitro* experiments, is just about the same. All these factors suggest that mare's milk, if available, would be particularly worth trying in infants intolerant of cow's milk. Reindeer, llama, water buffalo, and camel's milk have been used for feeding children. The same is true of the milk of the anthropoid ape which, as might be expected, is closer in composition to human milk than that of any other species of animal.[219]

Glaser contends that at present the best substitute for cow's milk, if soybean milk is not satisfactory, is prepared by using strained meats as the protein base. Rowe[176] first published formulas using beef and lamb meat juice in milk substitutes in 1931. The meat milks, which are essentially soups (just as soybean milk is essentially a bean soup), have a chemical composition very similar to that of cow's milk. The taste is pleasant and they are readily accepted by the infants. This author states that he has used them successfully as the sole milk substitute during the newborn period. The meat milks are easy to prepare, and Rowe's formula may be found in this article in Table I. This material, however, is now available commercially by Gerber and Swift and Company. Glaser states that at present experiments are under way using whale meat, now readily available in the American market, as the protein base for meat milks. No members of this family are widely used for food in this country, so congenital sensitivity to whale meat is not to be expected.

Collins-Williams[35] points out that the allergic reaction to cow's milk is becoming more and more important as breast feeding becomes less popular. He reports a case of acute allergic reaction to cow's milk in an infant under his care who was probably sensitized *in utero*. While the acute type is rare, the less severe reactions are common, as can be substantiated by a review of the literature. This patient had not received any cow's milk in the newborn nursery or at home until about two months of age, when he had severe vomiting and diarrhea following the ingestion of evaporated milk. The patient then had no further milk until a similar reaction at the age of six and one-half months. Collins-Williams believes that the best way to manage acute sensitivity to cow's milk is as follows:

1. *Attempts to prevent sensitization to cow's milk in the newborn infant.*—(a) The infant should be breast fed from the time of birth. (b) Occasional supplementary feedings of cow's milk should never be given. It should be a rule in all newborn nurseries that, if an infant is to be breast fed, any necessary supplement given before the flow of breast milk is well established should consist only of lactose or glucose water. If it is found necessary to use cow's milk either as a supplementary or sole feeding, this should be given in the form of evaporated milk, and once it has been started, it should be continued daily. (c) If minor sensitivities to cow's milk do appear, the evaporated milk should be withdrawn from the diet for at least several months and a milk substitute used. After a period of several months evaporated milk can then be tried in small quantities and gradually increased if tolerated.

2. *Treatment once acute sensitization to cow's milk has become manifest.*—(a) The infant should be breast fed if possible, the mother restricting her own milk intake to one or two glasses a day with supplementary calcium. (b) If the infant cannot be breast fed, a milk substitute should be used. Goat's milk may be used in the patients who have suffered allergic shock but had no other manifestations of allergy. (c) Once all symptoms of milk sensitivity have subsided, the infant should be started on an oral hyposensitization program with drop doses of pasteurized milk, which has been boiled for three minutes, increasing gradually as fast as possible without precipitating symptoms.

3. *Attempts to prevent acute milk sensitivity in subsequent offspring.*—(a) Throughout her pregnancy, the mother's intake of raw cow's milk should be restricted to two glasses a day with the addition of added calcium. (b) The infant, after birth, should be breast fed entirely. If this is impossible, a milk substitute should be used for the first few months of life and cow's milk rigidly avoided in any form, as has been repeatedly emphasized by Glaser. (c) Between three and six months of age, evaporated cow's milk may be tried, in small quantities at first.

The prophylaxis of allergic disease with reference to the newborn infant is an important procedure. For the purposes of prophylaxis, Glaser[68] defines, a potentially allergic child as one who has one or more allergic parents or siblings. He found in his practice that approximately 60 per cent of such children develop major allergic disorders, particularly eczema (atopic dermatitis), pollinosis, and/or asthma before they reach the age of six years.

As a preventive measure, this author instructs that pregnant mothers of potentially allergic infants should avoid eggs as such and foods consisting largely of egg, as custard, et cetera. It is also recommended that the prospective mothers drink not more than a pint of milk a day, boiled for ten minutes, and that they eat no cheese. They are instructed to make meats in variety their chief source of protein and to take added calcium and phosphorus to make up for what they do not get in milk. The same diet is given to the mother in those rare instances in which she can be persuaded to nurse her baby. If the mother will not or cannot nurse her baby, an attempt is made to start the infant on soybean or meat base milk. For these reasons, it is desirable to have readily available an adequate substitute for breast milk which should also be of reasonable cost. The milk of other animals, such as the goat, is not commonly satisfactory.

Glaser reports that the starting formula for the infants was usually one-third of a commercial soybean preparation (Mull-Soy) and two-thirds water, which was gradually increased to equal parts of soybean milk and water as the infants became accustomed to the formula. He warns that the feeding of the newborn should be undertaken only by those who are well trained in this respect. Soybean formulas are likely to cause diarrhea and irritation of the buttocks, which in newborn infants may become matters of serious concern. However, when diarrhea and/or sore buttocks appear, it is treated in the usual manner but, if unsuccessful, the soybean preparation is discontinued. Glaser reports that it was necessary in less than 15 per cent of his cases, however, and this includes

those infants in whom intractable colic and emesis also appeared to be due to the soybean feeding.

The results of this method of feeding, as far as the prophylaxis of allergic disease is concerned, far exceeded expectations. It is *a priori* reasoning that if one does not feed cow's milk to an infant, allergy to cow's milk does not occur. Glaser reports that only 8 per cent of their experimental group developed eczema as compared with about 30 per cent of the control group. The eczema in this 8 per cent of the cases, of course, was due to other factors than cow's milk. In a few instances, where there was a congenital sensitivity to cow's milk, the infants reacted when again fed cow's milk at an average age of six to nine months. In only one instance, however, was the milk sensitivity retained after further prolonged abstinence from cow's milk.

This investigator suggests that it is interesting to consider the often discussed problem as to whether or not allergic diseases are more common in children now than they were years ago. Unfortunately, there are no well-documented studies concerning this. However, if the observations of Grulee and Sanford to the effect that seven times as many bottle-fed babies develop eczema as compared with breast-fed babies are factual and if Glaser's observation that 8 per cent of infants with eczema later develop asthma or pollinosis or other allergic disease before the age of ten years are correct, then one may easily see why the progressive abandonment of breast feeding, which began in this country twenty-five or thirty years ago, could easily be responsible, at least in part, for the progressive increase of allergic disease in children if this, as many believe, has actually taken place. If this line of reasoning is not erroneous, the proponents of breast feeding are provided with a very potent argument in their support.

A belief seems to have become entrenched in the professional mind that infants and young children are not suitable subjects for comprehensive allergy diagnostic and management procedures. This group, therefore, has been neglected, and there is little data with respect to their allergic status according to Ranter and his co-workers[154] Infants and young children may outgrow their hypersensitivities spontaneously or they may develop an immunologic tolerance through continued natural contact. On the other hand, according to these investigators, allergy that appears in the very young may persist into adult life. A presentation of the findings in this age group, they believe, will encourage further intensive work and help to forestall or shorten the inroads of allergy in later years. The following is their report on a comprehensive investigation of sixty-four infants and preschool children. The allergic status was carried out in twenty-seven infants and thirty-seven children between the ages of two and five years with asthma, eczema, hay fever, or urticaria. The age of onset of allergy does not appear to be controlled by hereditary factors, for the incidence of inheritance in these young children was no greater than that found in other allergic persons. Seventeen (27 per cent) of the sixty-four patients gave evidence of congenital allergy (sensitization *in utero)* through skin tests by sensitivities to foods they had not previously ingested. According to these authors, it appears allergic diseases in young children show a predominance of eczema in the first years of life, followed by a fall in eczema and a rising incidence of asthma and hay fever as age progresses. They found no cases of true hay fever in children before the third year of life. However, pollen

asthma did occur before then. The incidence of causative factors in children, as they progressed in age, was characterized by a decreasing sensitivity to foods and an increasing sensitivity to pollen. The incidence of sensitivity to miscellaneous inhalations was relatively high, whereas that of mold sensitivity was moderate. It is interesting to note that in the first year of life, 100 per cent of the patients reacted to foods alone or in combination with other allergens, but by the fifth year this was reduced to 60 per cent.

Milk sensitivities occurred in eighteen patients (28 per cent), but none of these patients reacted to milk alone. Most of them reacted to the whey proteins but less than one quarter reacted to the casein fraction. Only this latter group required milk substitutes. Most of the milk reactors tolerated heat-treated milks. Thirty-one patients (48 per cent) reacted to egg proteins; thirty (46 per cent) reacted to one or more cereal grains, but none reacted to rice; eighteen (28 per cent) reacted to citrus fruits; thirty-seven (58 per cent) reacted to sea foods. Chocolate was shown to be an infrequent offender. Most of the miscellaneous inhalant sensitivities occurred with other sensitivities, but occasionally these inhalants were the sole offenders. Mold sensitivity always occurred in conjunction with other sensitivities. According to these investigators, nasal eosinophilia was an important aid in the early diagnosis of allergy and occurred in thirty-three (89 per cent) of the thirty-seven children who presented adequate smears for this type of study. Most patients responded well to a multifaceted therapy. This group of investigators warn that infants with allergy should be skin tested early and studied comprehensively. The rehabilitation of a young allergic cripple should forestall or shorten the inroads of allergy in later years.

An example of the way allergy is not infrequently treated is provided by the history of an asthmatic child of five years who was seen by Hill.[83] According to this clinician, the child had previously been treated in another city and brought with her a typed list, bound in the form of a small book, of the foods that she could and could not eat, as determined by skin tests. The "good" foods were typed in black, and the "bad" foods in red; it was all very impressive. She had been tested with 236 foods, including squab, tripe, calves' brain venison, caviar, poppy seed, elderberry pheasant, hops, chives and Limburger cheese, and had been found allergic to 109 of them, including Sanka coffee, rutabaga, German celery, thyme, cranberry, sand dab, tripe, sweetbreads and watercress. Among the foods she was allowed to eat were pheasant, guinea hen, venison, horse meat, turtle, abalone, terrapin, caraway seed, juniper, avocado, mango and quince. Hill found that the asthma was in reality due to grass and tree pollen, and she was later quite successfully hyposensitized, with no dietary restrictions whatever. This author states that this is by no means an isolated example and that too many people, without proper training or common sense, treat allergy in this way. Food allergy, in particular, lends itself to exploitation, for a dietary "cure" of any sort is a form of therapy that has made a great impression on the laity from time immemorial, and some of the greatest fads and misconceptions in medicine have had "diets" as their basis. He rightly contends that sensitization to food is a common cause of allergic symptoms is certainly true; that too much pseudo-science and too little common sense are too often used in dealing with foods as allergens is equally true.

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AMERICAN MEDICAL ASSOCIATION MEETING

Allergy Session

The co-chairmen of the session devoted to allergy of the 1957 meeting of the American Medical Association are Drs. Carl E. Arbesman and Ethan Allan Brown. The secretary is Dr. Clarence Bernstein. Those physicians who wish to present papers at the June meeting in New York City are requested to send abstracts of 250 words to the Secretary at 740 Magnolia Avenue, Orlando, Florida. Physicians whose papers are accepted will be notified at the earliest possible date.

How Your College Works

THE NOMINATING COMMITTEE

Although the appointed and elected officers are responsible for the smooth running of the College administration, the ultimate responsibility rests upon the Nominating Committee which helps to choose them.

The appointed officers are two, the Executive Vice President and Counsel, Mr. Eloi Bauers; and the Executive Treasurer, Dr. John D. Gillaspie. Both are appointed by the Board of Regents. In 1956, Dr. Gillaspie was elected Treasurer, because in that year the offices of Secretary and Treasurer were made separate.

It is the duty of the Nominating Committee to consider candidates for the offices of President-Elect, First and Second Vice Presidents, Secretary and Treasurer and three members of the Board of Regents. These choices are governed by a number of considerations, primarily the functions of each officer.

The President-Elect, while he holds office, is the Over-all Program Chairman and a member of the Board of Directors. These positions give him experience in all College activities and introduce him into the management of College business.

It is the President's chief duty to serve as Chairman of the Board of Regents, which meets during and after the Annual Congress, and at such times as circumstances make necessary. The President is also a member of the Board of Directors of which he becomes Chairman when his term of office as President has expired. The following year he becomes a member of the Finance Committee, and the second year after that, its Chairman. When the Nominating Committee chooses a candidate for President-Elect it must bear in mind that he will have one year of indoctrination as Program Chairman, and as a member of the Board of Directors, then one year in office followed by four years during which his knowledge and experience in every aspect of College administration are available to the other officers and the Fellows-at-Large.

The First Vice President presides in the absence of the President, but, he is also an active member of the Board of Directors, which, in addition, is composed of the immediate Past President (Chairman), the President, the President-Elect, and one elected member of the Board of Regents, then serving in his third term on that Board. The Nominating Committee, therefore being aware of his duties, chooses the candidate for First Vice President with great care, although he serves only for one year.

Although the Second Vice President has no official duties, the Nominating Committee chooses him for office on the basis that should any emergen-

cy arise he could assume the office of First Vice President, or, in special circumstances, that of the President.

The Secretary keeps the records of all meetings, sessions, and councils, as well as the minutes. He shares these duties with the Executive Vice President, who is always present with him. Only by this double-check can the College be certain that the letter and the spirit of all decisions following discussions and meetings are as planned.

The Treasurer, who is responsible for all financial transactions, is elected but an Executive Treasurer may also be appointed. The two positions may be held by one person. The Constitution and By-laws are in the process of amendment, so that the elected Treasurer may be re-elected, and therefore, succeed himself, as may the appointed Treasurer.

The Nominating Committee must also choose for candidates three Fellows to serve for three years on the Board of Regents. The Regents are ten in number, of whom three are Fellows respectively serving for their third year, three for their second and three for their first. The President is the tenth member.

With these responsibilities in mind the Fellowship of the College established a Constitution and By-laws stating that the Nominating Committee should consist of five Fellows. The President is Chairman, and the other members are two Past Presidents and two of the three Regents serving their third year, as chosen by the Board of Regents itself. To insure the continuity of the democratic process no member of the Nominating Committee may serve twice in succession. The President, who is Chairman, may not be chosen (by the new President) to serve as a Past President. No two Past Presidents may serve in succession, and, of course, the Regents being two out of three in their third year of service, cannot succeed themselves.

So that the Nominating Committee may be removed from the preceding, or next Annual Congresses, its first action is scheduled for not earlier than three months and not later than six months after its establishment. During the ninety days before its first meeting, it has access to, and scrutinizes, the College records. During this time, the Chairman circularizes the other four members requesting that names of candidates for each office be submitted.

The qualities necessary for the office, the qualifications of the candidate, and geographical representation of the Fellowship are all taken into consideration. As each member of the Committee sends in his list, the names which appear in each become part of a Master List. This is gradually shortened as the qualifications of each Fellow are carefully studied. The eventual decisions depend on screening, detailed examination of the aptitudes of the candidates, and thoughtful consideration before final selection.

Then, not less than three months before the ensuing election, official

notification of the slate must be published in the ANNALS OF ALLERGY or sent by mail to all voting Fellows. There are two other safeguards for the proper selection of officers: Any ten Fellows may nominate a slate and send it to the Secretary at least thirty days prior to the annual meeting. This gives the Secretary time to check the qualifications of these candidates, so that, if necessary, he can report on them at the annual meeting. And, in addition, candidates for any office may be nominated from the floor at any annual business meeting.

Election is by open, or by secret ballot, depending on whether there is one or more than one candidate for the office. The Nominating Committee does its best for the interests of the College. The final decisions, however, depend democratically upon the voting Fellows, in whose hands the future of The American College of Allergists truly rests.

. . . If we could obtain the value of a given exertion of nerve force by determining the quantity of electricity; or of heat, of which it is the equivalent; if we could ascertain upon what arrangement, or other condition of the molecules of matter, the manifestation of the nervous and muscular energies depends (and doubtless some day science will ascertain these points), physiologists would have attained their ultimate goal in this direction; they would have determined the relation of the motive force of animals to the other forms of force found in nature; and if the same process had been successfully performed for all the operations which are carried on in, and by, the animal frame, physiology would be perfect, and the facts of morphology and distribution would be deducible from the laws which physiologists had established, combined with those determining the condition of the surrounding universe.—T. H. HUXLEY: A Lobster; or The Study of Zoology. From *Discourses Biological and Zoological,* 1861.

* * *

In one day the multiplication of a microbe may result in a number with thirty figures. Were there an annual plant with only two seeds, it could be represented by over a million in the twenty-first year. But a common British weed *(Ssisymbrium officinale)* has often three-quarters of a million of seeds, so that in three years it could theoretically cover the whole earth. Huxley calculated that if the descendants of a single green fly all survived and multiplied, they would at the end of the first summer weigh down the population of China. A codfish is said to produce two million eggs, a conger eel ten million, an oyster twenty million. The starfish Luidia, according to Mortensen, produces two hundred million eggs every year of its life.—SIR J. ARTHUR THOMSON and PATRICK GEDDES: *Life: Outlines of General Biology,* 1931.

Papers of Interest

Riemer, A. D.: The effect of prednisone in the treatment of refractory cardiac edema. Bull. Johns Hopkins Hospital, 98:445 (June) 1956.

Prescribed for a patient suffering from myocardial infarctions, prednisone reduced edema and seemed to restore cardiac compensation.

Lapides, J., and Boyd, R. E.: The effect of intravenous Benadryl in allaying allergic manifestations of 70 per cent Urokon. J. Urol., 75:1016 (June), 1956.

In 1281 consecutive patients receiving intravenous Benadryl immediately prior to injection of 70 per cent Urokon no urticarial, asthmatic, or shock-like reactions were noted.

Leinassar, J. M.: Contact dermatitis due to chlorpromazine. Northwest Med., 55:661 (June) 1956.

Four nurses who had continuous, prolonged contact with chlorpromazine developed severe contact dermatitis.

Mussett, M. V., and Perry, W. L. M.: The second international standard for corticotrophin. Bull. World Health Organ., 14:543, 1956.

Twelve laboratories in five countries collaborated to assay ACTH by three methods and agreed that 1 international unit equals 0.88 mg.

Brodish, A., and Long, C. N. H.: Estimation of blood ACTH by means of a cross-circulation technique. Yale J. Biol. Med., 28:650 (June) 1956.

Useful technique for research workers in the field of allergy.

Williamson, B.: Simplified dosage. Lancet 2:97 (July 14) 1956.

A plea for the extension of the unit system used for penicillin, insulin and vitamins to all drugs.

Andrews, B. E.; McDonald, J. C.; Thorburn, W. B.; and Wilson, J. S.: Respiratory virus infection in Royal Air Force 1954-55 with particular reference to influenza and A.P.C. viruses. Brit. Med. J., 1:1203 (May 26) 1956.

At one time or another approximately one-seventh of the personnel suffered from respiratory tract infection. Identifiable virus infections other than influenza B were responsible for comparatively little illness. Less than 1 per cent showed evidence of A.P.C. virus infection.

Panzani, R.: The provocation of dyspnea with acetylcholine as a diagnostic test for respiratory allergy. (Test de la dyspnée provoquée par l'acétylcholine et diagnostic de l'allergie respiratoire.) Internat. Arch. Allergy & Appl. Immunol., 7:25-41, 1955.

The degree of dyspnea produced by acetylcholine may help to diagnose minor and atypical forms of respiratory allergy. The drug is administered in aerosol form, a 1 per cent solution for one to three minutes, and spirometric recordings are obtained after forced expiration. A change from the patient's pretreatment vital capacity shows a reduction in those suffering from allergic disorders of the respiratory tract, neurodermatitis, and emphysema.

Eriksson-Lihr, Z.: Special features in allergy in children. [In English] Acta allerg. (Kbh.), 8:289-313, 1955.

The author reviews the records of nearly 30,000 children in Helsinki, and 4,382 school children in Türkü. The incidence of asthma was higher in boys and eczema higher in girls. The allergic factor was more important in the former and the infectious factor in the latter. The author suggests that the function of the adrenal cortex in boys is inferior to that of girls.

Ames, F.: The hyperventilation syndrome. J. Ment. Sci., 101:466-525 (July) 1955.

A full discussion of the physiologic and psychiatric aspects of the hyperventilation syndrome.

Wedgwood, R. J. P., and Klaus, M. H.: Anaphylactoid purpura (Schönlein-Henoch Syndrome). A long-term follow-up study with special reference to renal involvement. Pediatrics, 16:196-206 (August) 1955.

Out of thirty-six children admitted to the Babies' and Children's Hospital, Cleveland, Ohio, with anaphylactic purpura in 1936-1953, twenty-six were re-examined in 1954. In ten, urinary abnormalities were found (latent nephritis). A mild or unnoticed attack of anaphylactic purpura may be the cause of unexplained chronic nephritis in adults.

Sinclair, J. D.. The effect of breathing exercises in pulmonary emphysema. Thorax, 10:246-249 (Sept.) 1955.

In thirty-one patients with clinical, radiographic and physiologic signs of emphysema, the response to the usual breathing exercises was assessed by standard tests of pulmonary function. There was no correlation between the degree of subjective improvement and the results of any of the standard tests. It is suggested that the relief of dyspnea is due to elimination of wasteful inspiratory effort.

Green, A. F., and Ward, N. B.: The action of analgesics and nalorphine on the cough reflex. Brit. J. Pharmacol., 10:418-423 (Dec.) 1955.

The antitussive properties of morphine, codeine, pethidine, amidone, piperidylamidone, thiambutene, pholcodine, narcotine, and nalorphine were studied. In cats, a cough reflex was induced in one of three ways: by electrical stimulation of the central end of the cut superior laryngeal nerve, by introduction of an intratracheal tube, or by insufflation of sulphur dioxide. Amidone was the most powerful suppressant of coughs caused by electrical stimulation, having eight times the antitussive effect of morphine, twenty times that of codeine.

PAPERS OF INTEREST

JENSEN, F.: Past history and skin reactions in allergic children. Acta allerg. (Kbh.), 9:188-202, 1955.

The skin reactions of 600 children with allergic diseases, mainly asthma, were investigated between 1948-52, to determine their relation to allergic symptoms. House dust, feathers, molds, and grass pollens were the most important inhalant allergens.

Tiffeneau, R.: A pharmacodynamic test for the assessment of severity in asthma. Estimation of the excitability of the lung by acetylcholine. (Evaluation du degré de l'asthme par une epreuve pharmacodynamique. La mesure de l'excitabilité acetylcholinique du poumon.) Ann. méd., 56:582-602, 1955.

An aerosol of acetylcholine was administered to asthmatic patients and the threshold doses which produced a lowering of the vital capacity at rest and after effort were observed. The sensitivity to acetylcholine was highest in those with chronic asthma and emphysema. The acetylcholine sensitivity test may help differentiate this type of case from asthmatic emphysema in which no change of tolerance to acetylcholine is found.

Frankland, A. W.: High and low pollen extract treatment in summer hay fever and asthma. [In English.] Acta allerg. (Kbh.), 9:183-187, 1955.

A comparison was made between two groups of patients with hay fever, who were treated preseasonally with pollen extract to a maximum dose, on the one hand, of 100 Noon units (low-dosage group), and on the other, 18,000 units (high-dosage group). In hay-fever and pollen asthma preseasonal treatment aiming at a maximum dose of 18,000 units gives significantly better results than a low-dosage scheme.

Frankland, A. W.; Hughes, W. H.; and Gorrill, R. H.: Autogenous bacterial vaccines in treatment of asthma. Brit. Med. J., 2:941-944 (Oct.) 1955.

This investigation was made to determine whether or not bacterial vaccines are specifically helpful in the treatment of asthma. Results were not appreciably different in the two groups: more than half of both treated patients and controls were improved; twenty-four of the treated patients and twenty-five (out of eighty-four) controls were unchanged, while eighteen of the former group and fifteen of the latter were worse. Results were proportionately similar in those who were selected for injections but did not actually receive them.

Robinson, H. M., and Hollander, B.: Topical use of chlorquinaldol. J. Invest. Dermat., 26:143 (Feb.) 1956.

In 756 patients, chlorquinaldol (Sterosan,® Geigy) was effective in skin disorders complicated by secondary infection. It was useful in the treatment of atopic dermatitis, seborrheic dermatitis, and psoriasis. It was not otherwise effective.

Lubowe, I. I.: A therapeutic evaluation of hydrocortisone and oxytetracycline hydrocortisone in cutaneous diseases. Am. Practitioner, 7:962 (June) 1956.

Hydrocortisone 1 per cent, and oxytetracycline 3 per cent in ointment form, "cured" twenty-five of forty-four patients with dermatoses. Nineteen patients showed clinical improvement.

Haxthausen, A.: A comparison of the inhibitory effect of 9*a*-fluor-hydrocortisone acetate ointments on eczematous reactions produced by electrophoresis. J. Invest. Dermat., 26:111 (Feb.) 1956.

The most effective compound in suppressing the reactions was the 9*a*-fluor-hydrocortisone acetate.

Chakravarty, N. K.; Natallana, A.; Jensen, R.; and Borison, H. L.: Central effects of antitussive drugs on cough and respiration. J. Pharmacol. & Exper. Therap., 117:127 (June) 1956.

The effects on cough, inspiration, and pulmonary ventilation of antitussive agents were determined in rats, some decerebrated, some given pentobarbital.

Hunter, F. E., Jr., and Lowry, O. H.: The effects of drugs on enzyme systems. Pharmacol. Rev., 8:89 (March) 1956.

Many drug-enzyme interactions are complex. A review with 249 references.

Pastor, B. H., and Tetreault, A. F.: Agranulocytosis and scarlatiniform eruptions due to phenindione. J.A.M.A., 161:873 (June 30) 1956.

Agranulocytosis is a serious but rare sequel to anticoagulant therapy with phenindione.

Meier, R., et al: Antiallergic activity of bacterial polysacharrides. Experientia, 12:235 (June) 1956.

Some bacterial polysaccharides demonstrate marked antiphylactic properties.

Bawnik, J. B.: Treatment of icteric pruritus with antihistaminics. Preliminary report. Prensa méd., Argent., 43:580, 1956.

Of 100 patients suffering from icteric pruritus, fifteen were treated with intravenous Benadryl and other antihistaminic agents taken orally. Relief was quick and complete.

Hilleman, M. R.; Stallones, R. A.; Gauld, R. L.; Warfield, M. S.; and Anderson, S. A. Prevention of acute respiratory illness in recruits by adenovirus (RI-APC-ARD) vaccine. Proc. Soc. Exper. Biol. & Med., 92:377 (June) 1956.

A report of the development, preparation and clinical evaluation of an effective vaccine against respiratory illnesses caused by viruses of the adenovirus group.

Origin of antibodies. Lancet 1:89 (January 14) 1956.

No single organ can be identified as the sole producer of antibodies, nor are they produced at the site of infection or injection, although they are demonstrable in the lymph glands. A plasma cell or its precursor may be the responsible tissue. An actual review of the present state of this controversial subject.

News Items

NOTICE OF ELECTION OF OFFICERS AND REGENTS THE AMERICAN COLLEGE OF ALLERGISTS

The Nominating Committee has selected one candidate for each elective office to be voted on at the next annual election in accordance with the By Laws of The American College of Allergists, Article V, Section 7 (j), which reads as follows:

"Article V, Section 7 (j).—The Nomination of Officers.—The Nominating Committee shall be composed of five (5) members: The President, two (2) members of the Board of Regents each of whom has served at least two (2) years on the Board, and two (2) past Presidents, both Regents and Past Presidents to be selected by the Board. *No member may serve on this committee for two consecutive years.* Not earlier than three (3) months, but not more than six (6) months after its selection the Nominating Committee shall pick one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing, and accomplishments in the field of allergy of those considered for selection, and all information contained in the membership records maintained in the Secretary's office as to any proposed selectees shall be seasonably supplied to the Committee for this purpose. The Nominating Committee shall report its selections to the Secretary's office and as soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary, provided said additional nominations are received in the office of the Secretary at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting."

Nominating Committee
ETHAN ALLAN BROWN, *Chairman*
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FREE ALLERGY CLINIC

The first free allergy clinic for indigent patients was opened July 24, 1956, at the Ohio Valley General Hospital, Wheeling, West Virginia. With the kind permission of the medical director, Dr. M. B. Williams, the interns and medical residents will participate. Dr. Martin D. Reiter, F.A.C.A., will be in charge. This is the first teaching allergy clinic in the state of West Virginia.

NEW ASSOCIATE MEMBERS

The following physicians have been elected to associate membership in The American College of Allergists in the period, April 1 to July 30, 1956:

Alex Keith Barrett, M.D.
50 East 78th Street
New York 21, New York

Stanford Borne, M.D.
29 South Cottage Street
Valley Stream, Long Island, New York

Stanley Cohen, M.D.
1441 Delachaise
New Orleans, Louisiana

Albert Graham Davis, M.D.
307 Gas and Electric Building
Utica 2, New York

Frederick Fischler, M.D.
Lake Avenue
Saint James, New York

Alf Cornelius Johnson, M.D.
Great Falls Clinic
Great Falls, Montana

Stephen J. Karpinski, M.D.
132 North Street
Auburn, New York

Arnold F. Laverstein, M.D.
6721 Reisterstown Road
Baltimore 15, Maryland

Donald Lewis, M.D.
738 Broadway
Seattle, Washington

Arthur Lipschutz, M.D.
7974 Fayette Street
Philadelphia 50, Pennsylvania

Marshall Mandell, M.D.
7 Washington
South Norwalk, Connecticut

Charles A. Minnefor, M.D.
1164 South Orange Avenue
South Orange, New Jersey

Robert Branstrom Olney, M.D.
1019 Gayley Avenue
Los Angeles 24, California

Melvin Smoley, M.D.
17 Astronomy Lane
Levittown, New York

Robert W. Raymond, M.D.
75 Willett Street
Albany, New York

Philip Schneider, M.D.
114-06 Queens Boulevard
Forest Hills 75, New York

Eduardo A. Tschen, M.D.
50 East 78th Street
New York 21, New York

SUBCOMMITTEE ON ENTOMOLOGY

Any College member desiring to work on the Subcommittee on Entomology, Committee on Aerobiology, should communicate with the subcommittee chairman, Dr. Boen Swinny, 314-320 Medical Arts Building, San Antonio 5, Texas.

CONSULTANT APPOINTED

Dr. Jules Freund, Chief of the Division of Applied Immunology, The Public Health Research Institute of the City of New York, has been appointed a consultant to the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, to assist in establishing its new Allergy-Immunology program.

The experience and advice of Dr. Freund, leader in investigations in basic immunology and recognized throughout the world as outstanding in his field, will be utilized in the selection and evaluation of young investigators and in determining the methods of approach to pertinent problems in this area of research.

RESIDENCY IN ALLERGY, OHIO STATE UNIVERSITY HEALTH CENTER

A fully accredited one-year residency in allergy is open to those who have had an internship and two years residency in medicine. Clinical and private, adult and children, in-and-out patient services are available.

For further details, write John H. Mitchell, M.D., 1625 Perry Street, Columbus, Ohio.

CHICAGO SOCIETY OF ALLERGY

The new officers of the Chicago Society of Allergy for the year 1956 to 1957 are as follows:

Helen C. Hayden, M.D.....President
Norman J. Ehrlich, M.D.....President-Elect
Harold C. Wagner, M.D.....Secretary-Treasurer

MICHIGAN ALLERGY SOCIETY

The newly elected officers of the Michigan Allergy Society are as follows: President, Kenneth P. Mathews, M.D., Ann Arbor; vice president, E. Oskar Schreiber, M.D., Flint; secretary-treasurer, Bernard Dickstein, M.D., Flint; additional executive committee members: Henry D. Beale, M.D., Toledo, Ohio; Sidney Friedlaender, M.D., Detroit; and Joseph H. Shaffer, M.D., Detroit.

WASHINGTON STATE SOCIETY OF ALLERGY

The Washington State Society of Allergy has recently elected the following officers:
President.....Robert A. Stier, M.D., Spokane, Washington
Vice President.....Howard L. Hull, M.D., Yakima, Washington
Secretary-Treasurer.....Lois Frayser, M.D., Seattle, Washington

WOMEN'S AUXILIARY OFFERS TWO PRIZES

The Women's Auxiliary of The American College of Allergists announces, for the second time, that at the Thirteenth Annual Meeting of The American College of Allergists two prizes will be offered.

THE BELA SCHICK AWARD: A prize of $150.00 and a Certificate of Merit for the best paper written by an Associate Fellow of The American College of Allergists to be presented at the Annual Convention of the College, March 20-22, 1957.

THE CLEMENS VON PIRQUET AWARD: A prize of $75.00, plus an additional $75.00 to defray traveling expenses to the Convention, together with a Certificate of Merit, will be awarded for the best paper written by an intern or resident on any aspect of allergy, to be presented at the Annual Convention of the College, March 20-22, 1957.

All papers submitted are to be judged by a committee consisting of the program committee of the annual College convention and members of the editorial board of the ANNALS OF ALLERGY.

ESSAY CONTEST—AMERICAN COLLEGE OF CHEST PHYSICIANS

The Council on Undergraduate Medical Education of the American College of Chest Physicians offers three cash awards annually for the best contributions prepared by undergraduate medical students on any phase in the diagnosis and treatment of chest diseases (heart and/or lungs). For the 1957 contest the first prize will be $500; second prize will be $300; and third prize $200. Each winner will also receive a certificate of merit. The winning contributions will be selected by a committee of chest specialists and will be announced at the 23rd Annual Meeting of the American College of Chest Physicians to be held in New York City, May 29 to June 2, 1957.

An application form must be completed, which may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A. Five copies of the manuscript typewritten in English (double spaced) should be submitted to the College offices in Chicago not later than April 10, 1957. The only means of identification of the author shall be a motto or other device on the title page and a sealed envelope bearing the same motto on the outside, enclosing the name and address of the author.

BOOK REVIEWS

EXPERIMENTAL TUBERCULOSIS BACILLUS AND HOST. Addendum on experimental leprosy. Editors: G. E. W. Wolstenholme and Margaret P. Cameron. Ciba Foundation Symposium. xii and 396 pages. Boston: Little, Brown and Company, 1955. $9.00.

This is a symposium provided for American and European workers by the Ciba Foundation. It is chiefly focused on the chemistry of the tubercle bacillus and the host's immunologic and tissue reaction to the bacillus and its components. The emphasis is on current work being done concerning the disentanglement of the enormously complex constituents of the genus Mycobacterium and its role in the interplay between infecting organism and host. It offers a splendid review of the present status of this work. Its advantage over more formal presentations is that it gives a lively report not only of established facts, but of working hypotheses and approaches, of experiments that did not yield positive results, or aborted. The viewpoints of the research team on their coworkers' achievements are well presented. Many minor factual data inaccessible elsewhere are found in these pages. The final chapters are concerned with the problems of research in leprosy and the relation of this infection to tuberculosis.

ACCIDENTS THERAPEUTIQUES EN DERMATOLOGIE. Jacques Charpy. 342 pages, 2000 fr. Paris, France: Masson et Cie.

This excellent volume contains much of interest to the allergist. The title is perhaps a trifle misleading, for the therapeutic accidents described are seen in most branches of medicine. The subject matter may be illustrated by reference to some of the articles contained: Cutaneous skin reactions due to internal medications; general accidents due to chemical and antibiotic drugs; Shwartzman reaction; reactions due to synthetic antihistamines and antimalarials; fixed drug eruptions; reaction to antileprous and antiepileptic drugs; clinical and statistical observations of drug intolerance in the Centre Allergolique de Turin; several articles on mycoses in relation to antibiotic therapy and, finally, a chapter on responses of normal and eczematous skins to varying concentrations of antibiotics.

This book brings together the papers read at the Fifth Colloquium of the Marseille affiliate of the French Society of Dermatology and Syphilology, under the directions of Prof. Jacques Charpy. The authors are among the most distinguished in France, and the quality of the papers illustrates that their fame is well founded. In general, the bibliographies are excellent and from world-wide journals. An occasional author is guilty of the common American fault of intellectual chauvinism and refers only to French language articles. The volume is highly recommended to all interested in drug allergy.—*V.J.D.*

THE PRACTICE OF PSYCHOSOMATIC MEDICINE AS ILLUSTRATED IN ALLERGY. Hyman Miller, M.D., and Dorothy Baruch, Ph.D. 196 pages, including index. McGraw-Hill, 1956. Price $5.00.

The authors of this volume are well known to readers of the ANNALS. Dr. Miller is a very competent allergist who in recent years has become intensely interested in the psychogenic factor in allergy. Dr. Baruch holds a Ph.D. in education and pioneered in modern nursery school teaching methods. She has written a large number of books dealing mostly with the problems of childhood. With the aid of her husband, Dr. Miller, she has also written a novel based on the story of an

asthmatic child. Both are intelligent individuals, very charming, and with a great flare for writing. Until Dr. Miller became involved in psychotherapy and the psychologic interpretation of allergic diseases, he performed many important scientific allergy investigations and his articles appeared in our leading allergy journals. It, therefore, is regrettable and unfortunate that a book such as *The Practice of Psychosomatic Medicine as Illustrated in Allergy* bears the names of these two fine people as authors. The book gives every evidence of having been published solely for its sales appeal.

The very title obviously was chosen to appeal to the largest number of readers. Indeed, this is candidly expressed by the authors and publishers, who in the preface and on the jacket of the volume state that it is "for the General Practitioner, Allergist, Internist, Pediatrician, Dermatologist, Otolaryngologist, Chest Physician, Psychiatrist, Psychoanalyst, Clinical Psychologist, and the Social Worker." When a book is written for such a wide audience, it is safe to assume that it will not be approved by all groups. In this case, it is problematic that it will be acceptable to the scientific member of any of these groups. In this reviewer's opinion, the only class of individuals who might enjoy reading this volume would be members of the laity who relish case histories peppered with sexual fantasies, sexual experiences, and the like. In these, the book abounds. Also, the actual writing would seem to indicate that the authors had lay people in mind. For example, they describe a headache as an "aching head (that) may spring from an aching heart." (p. 3). This is the kind of phraseology that is used throughout the book and sets its tone.

The first sentence in the preface also gives the physician an idea of what to expect. It reads as follows: "With the increasing awareness among patients as well as among physicians that allergy is psychosomatic . . . we feel that this book is a timely one." Throughout the book, terms, which to many have come to be considered "psychoanalytic jargon," are used. Thus, such phrases as "affect hunger," "need for self-punishment," "blocking of anger," "hostility against himself," "hostility turned onto himself," "indirect hostility," "displaced hostility," "maternal rejection," et cetera, are repeatedly encountered as explanations for the onset of asthma, eczema, hay fever, or whatever allergic disease is being discussed. The authors use statistics and case histories to substantiate their conclusions. Their statistics are nearly all 100 per cent. Here are some instances: 97 per cent of allergic children "had been living in an emotional climate where maternal rejection prevailed." (p. 32); 96 per cent of the mothers who rejected their children did so "before the onset of the child's illness." One hundred of 119 mothers who rejected their children "each had felt herself rejected." (p. 24); "Of these 119 mothers with attitudes of rejection, eighty-seven told of sexual maladjustments." (p. 34). They mentioned such things as their husband's impotence, premature ejaculations, demands for too frequent intercourse or too little intercourse. In by far the greatest number of these cases, however, the women's own dislike of the sex act accompanied by lack of orgasm was central. In sixty-eight individuals, seventy-seven traumatic occurrences were noted by the authors as immediately preceding an initial attack of a given syndrome. (p. 48). These included loss or threatened loss of parent, eruptive episodes of marital conflict, children witnessing sexual intercourse, sibling rivalry, oversevere habit training, masturbation threats by parents, physical violence by parents, and surgery. (pp. 48-52). This almost consistent 100 per cent incidence in the studies of Miller and Baruch, instead of corroborating their conclusions, leads one to doubt their verity. Such figures are seldom, if ever, found in clinical studies.

The case histories, for the most part, are excerpts of conversation by children. Many of them sound strangely like fiction and some are quite fantastic as an explanation of the "trigger mechanism" in allergic disease. An example, taken at

random, is the case history of a five-year-old boy. He "felt that if his penis were as big as his father's he might have the same privileges as his father (intercourse with his mother), and he had fantasies of wanting to bite off his father's organ . . . but he did not dare. Into his play, however, came many fantasies of sniffing his father's smell up to his nose. And along with such fantasies would go the hay fever attacks. His asthma also returned. . . ." (p. 63). According to the authors, "such fantasies of the nose being stuffed with anal material are the most frequent fantasies observed in the allergic child with hay fever." Other case histories are related in an attempt to validate Miller and Baruch's claims that children's anal fantasies, penis envy, or fear of losing the penis are associated with asthma and eczema in later life. These are statements with which only psychoanalysts of a particular school will agree.

Throughout the book there is displayed by the authors a deep appreciation of children's fears of tests and of injections. Their approach to their patients is one of kindliness and understanding. In this attitude toward patients, there will be complete agreement by the profession, generally; but, it is not sufficient to raise the standard of the work, or to make it acceptable as a text for the large class of well-trained, practicing allergists or scrupulously exacting psychiatrists, let alone scientifically-minded members of any of the groups to which it is directed.

JAMA CLINICAL ABSTRACTS OF DIAGNOSIS AND TREATMENT. Selected by Noah D. Fabricant, M.D., Editorial Associate, Journal of the American Medical Association. 661 pages, including index. New York and London: Grune and Stratton, Inc. 1956. Price $5.50.

The science of the diagnosis and treatment of disease is increasing so rapidly that no modern physician who wishes to keep abreast of the times can conceivably practice unless he makes himself familiar with the literature of his specialty. Unfortunately, an allergist must cull his material from varied journals, including those concerned with the nose and throat, and the remainder of the respiratory system, and the skin. His interests may range from immunology to dietary management, and from therapeutics to psychosomatic medicine. Above and beyond his specialty, he likes to know what is going on in other fields of medicine.

The abstracts published in the JAMA have always been famous for the excellence of their form, and the clarity of their language. Although there will be a great deal in these 661 pages which will not interest the allergist, on the other hand, there is much outside of his subject that he will enjoy reading.

Since in many cases he is the patient's only physician, he must keep abreast of his general medicine, however little he may use it. Although the book is not printed to be read for its continuity, it nevertheless, presents a broad and honest picture of medicine as it is practiced today.

COLLAGEN DISEASES. John H. Talbott, M.D., Professor of Medicine, The University of Buffalo School of Medicine; Physician-in-Chief, Buffalo General Hospital, Buffalo, New York; and R. Moleres Ferrandis, M.D., Training Fellow in Arthritis of the Western New York Chapter of the Arthritis and Rheumatism Foundation. 232 pages including index and bibliography, illus. New York and London: Grune and Stratton, 1956. Price $6.50.

The authors are to be congratulated on compressing so much factual material into 191 pages of text, and twenty-four pages (540 references) of bibliography.

Although systemic lupus erythematosus is not common, the internist practicing allergy will want to remember that pleuropulmonary signs and symptoms occur in over eighty per cent of the patients. "A hacking cough, sometimes dry, sometimes productive, and a few fine or coarse rales, may be the only signs of parenchymal involvement."

The reader will need no reminding or need to remember that many cases of polyarteritis are seen by allergists with increasing frequency. With each passing year, the literature becomes more and more sure of the etiology as a hypersensitivity to drugs. Among others, an association with administration of sulfonamides, penicillin, Dilantin, mercury, arsenicals, thiourea, iodine and cortisone, and ACTH has been stressed. In one series, an incidence of bronchial asthma of 12 per cent was discovered; and in the second of 300 patients, the incidence of bronchial asthma was eighteen per cent; while in the third series of 175 cases, it was twenty-five per cent. In a hypersensitive, infected male asthmatic patient who has low grade fever and an eosinophil count of fifteen per cent, or more, the diagnosis must always be kept in mind.

The chapters on dermatomyositis and systemic scleroderma are well written but not likely to be of interest to allergists. On the other hand, the chapter on thrombotic thrombocytopenic purpura emphasizes the possibility of an allergic cause, bacterial or drug.

The color plates and roentgenograms are extremely well done.

The authors state that had the book been encyclopedic or exhaustive in scope, they might have included serum sickness, Loeffler's pneumonia, thromboangiitis obliterans, ulcerative colitis, glomerulonephritis, drug-group incompatability, malignant hypertension, erythema nodosum, erythema multiforme, pemphigus, and anaphylactoid purpura, which have been classed by some investigators as collagen disorders. They have, however, limited themselves to the five disorders in which proof of collagen dyscrasia was most certain.—*E.A.B.*

"I had also, during many years followed a golden rule, namely, that whenever a published fact, a new observation or thought came across me, which was opposed to my general results, to make a memorandum of it without fail and at once; for I had found by experience that such facts and thoughts were far more apt to escape from the memory than favorable ones."—*Darwinisms.*

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